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INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Donald L.	HERTZOG	Durham, North Carolina

☐ *Additional inventors are being named on the ___ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

HETEROCYCLIC MCHR1 ANTAGONISTS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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☒ No.
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Respectfully submitted,

SIGNATURE Bonnie L. Deppenbrock

Date 4/11/2003

TYPED or PRINTED NAME Bonnie L. Deppenbrock

REGISTRATION NO. (if appropriate) 28,209

TELEPHONE (919) 483-1577

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HETEROCYCLIC MCHR1 ANTAGONISTS

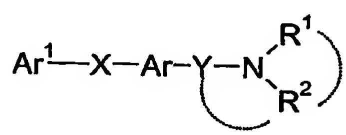
This invention relates to novel heterocycles which are antagonists at the melanin-concentrating hormone receptor 1 (MCHR1), also referred to as 11CBy, to pharmaceutical compositions containing them, to processes for their preparation, and to their use in therapy.

BACKGROUND OF THE INVENTION

Obesity is a medical condition that is reaching epidemic proportions among humans in a number of countries throughout the world. It is a condition that is also associated with or induces other diseases or conditions that disrupt life activities and lifestyles. Obesity is recognized as a serious risk factor for other diseases and conditions such as diabetes, hypertension, and arteriosclerosis. It is also known that increased body weight due to obesity can place a burden on joints, such as knee joints, causing arthritis, pain, and stiffness.

Because overeating and obesity have become such a problem in the general population, many individuals are now interested in losing weight, reducing weight, and/or maintaining a healthy body weight and desirable lifestyle.

WO01/21577 (Takeda) relates to a compound of the formula



wherein Ar^1 is a cyclic group which may have substituents, X is a spacer having a main chain of 1 to 6 atoms, Y is a bond or a spacer having a main chain of 1 to 6 atoms, Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents; R^1 and R^2 are independently hydrogen or a hydrocarbon group which may have substituents; R^1 and R^2 together with the adjacent nitrogen atom may form a nitrogen containing hetero ring which may have substituents; R^2 may form a spiro ring together with Ar; or R^2 together with the

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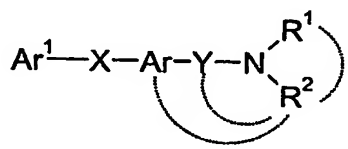
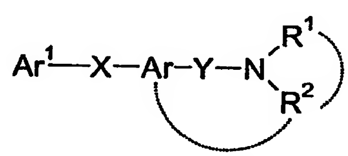
adjacent nitrogen atom may form a nitrogen containing hetero ring which may have substituents; or a salt thereof; and which compounds are antagonists of a melanin-concentrating hormone. Such compounds are suggested as being useful for preventing or treating obesity.

WO 01/82925A1 (Takeda) relates to a compound of the formula



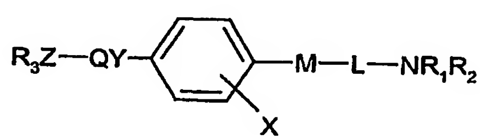
wherein Ar^1 is an optionally substituted cyclic group;
X and Y are the same or different spacers having from 1 to 6 atoms in the main chain;
Ar is an optionally substituted fused polycyclic aromatic ring;
R^1 and R^2 are the same or different hydrogen atoms or optionally substituted hydrocarbon groups, or R^1 and R^2 together with the adjacent nitrogen atoms may form an optionally substituted nitrogenous heterocycle, R^2 together with the adjacent nitrogen atom and Y may form an optionally substituted nitrogenous heterocycle, or R^2 together with the adjacent nitrogen atom, Y, and Ar may form an optionally substituted nitrogenous heterocycle or salts thereof.

WO 01/21577A2 (Takeda) relates to aromatic compounds of the formula



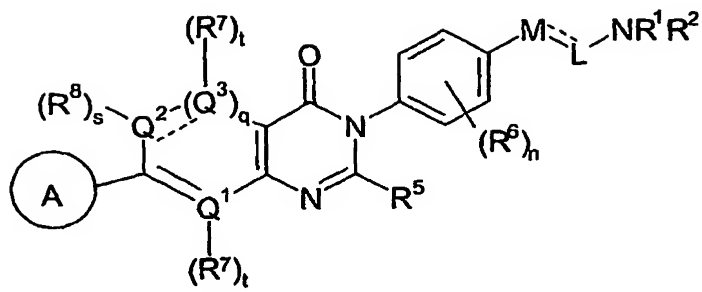
or a salt thereof, which is useful as an agent for preventing or treating obesity.

P32897WO1 (GlaxoSmithKline) relates to compounds of the formula



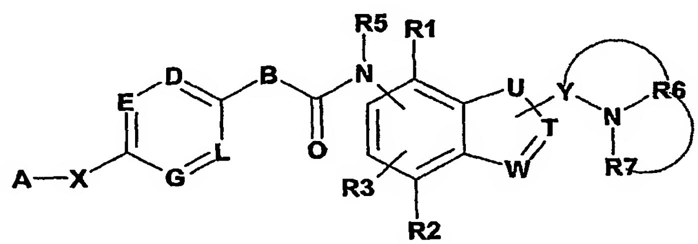
or a salt thereof , wherein M is a group selected from O, S, CO, NH or CH_2, L is a 2 or 3 membered alkylene chain, and the chain -M-L may be optionally substituted by one or more groups selected from methyl, ethyl, hydroxy or alkoxy and or which chain may contain a -C=C- double bond; R_1 and R_2 each independently represent hydrogen, C_{1-6} straight or branched alkyl which may be optionally substituted by phenyl, or C_{3-6} cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups; or R_1 and R_2 together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclic ring or a 7-10 membered bridged heterocyclic ring, which rings may be optionally substituted by a phenyl group or up to 4 C_{1-3} alkyl groups; or R_1 or R_2 may be linked to the group L or be linked as part of the substituted X on the phenyl ring to form a cyclic group; the group X may be linked to the group L to form a cyclic group which may contain an additional oxygen, a sulphur or nitrogen atom, alternatively or additionally there may be one or more substituents X selected from hydroxy, C_{1-2} alkyl, C_{1-2} alkoxy, halogen, C_{2-3} alkenyl, benzyl, CR_aNOR_b wherein R_a and R_b are independently hydrogen or methyl, methoxy-methyl, methoxymethoxy or methoxyethoxy; QY is a bicyclic fused heterocyclic ring wherein Y is one ring of a bicyclic fused heterocyclic group and which is linked via nitrogen atom therein to the phenyl ring, and substituted on the second ring Q by the group ZR_3; Z is a bond or a group selected from NH, NCH_3 O, S or CH_2; R_3 is a group selected from aryl, 2-alkenyl, cycloalkyl or 2-cycloalkenyl and which R_3 group may be optionally substituted by one or more C_{1-3} alkyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-3} alkoxy, cyano, trifluoromethyl or methylthio groups, processes for their preparation, pharmaceutical compositions containing them and to their use in medicine.

P32897WO2 (GlaxoSmithKline) relates to a compound of the formula comprising:



a pharmaceutically acceptable salt or solvate thereof, formulations, processes of preparing, and methods of administering to mammals are provided.

Aventis WO 03/015769A1 relates to aminoalkyl-substituted aromatic compounds of the formula below, their physiologically funcitonal derivatives and salts, as well as a method for a the production thereof. Said compounds can be suitably used as anorectic drugs.

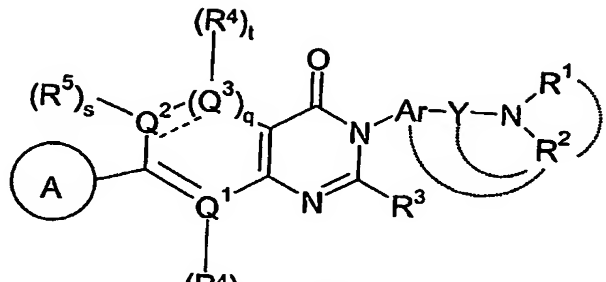


In particular, it is known that melanin-concentrating hormone ("MCH") originates in the hypothalamus and has orexigenic action (see Nature, Vol. 396, p. 670, (1998), for example). There is an on-going need for the development of a melanin-concentrating hormone antagonist useful in the treatment of obesity and other associated or related diseases and conditions.

Accordingly, we have now found a novel group of heterocycles that exhibit a useful profile of activity as antagonists of the melanin-concentrating hormone receptor (MCHR1) disclosed in Nature, Vol. 400, p. 261-265 (1999).

SUMMARY OF THE INVENTION

The present invention provides a compound of formula (I) comprising:



(I)

a pharmaceutically acceptable salt, solvate, or phyisiologically functional derivative thereof, wherein:

(A) is aryl or heteroaryl, optionally substituted one to four times by a least one substiutent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano, and alkylthio groups;

the dashed line connecting Q^2 to Q^3 represents an optional bond;

q, r, s, and t are each independently 0 or 1;

when q is 1, the bond between Q^2 and Q^3 is a double bond;

Q^1 and Q^3 are each independently C or N;

when q is 0 then Q^2 is N, S, or O;

when q is 1, then Q^2 is C or N; when q is 1 and Q^2 is N, then s is 0;

when Q^2 is S or O, s is 0;

when Q^1 is N, r is 0;

when Q^3 is N, t is 0;

R^3 is selected from the group consisting of hydrogen, amino, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, and C_{1-3} alkylthio;

when Q^1 or Q^3 is C, then each corresponding R^4 is independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo;

when q is 1 and Q^2 is C or when q is 0 and Q^2 is N, then R^5 is selected from hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo;

Ar is a fused bicyclic ring optionally substituted one to four times by at least one substituent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano, and alkylthio groups;

Y is a bond or a C_{1-6} alkylene, optionally substituted;

(i) R^1 and R^2 each independently are selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, and a 5- or 6-membered heterocycle wherein said alkyl, said cycloalkyl, and said heterocycle are optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, hydroxy, oxo (i.e., =O), alkoxy and halo;

or (ii) R^1 and R^2 may be selected from the group consisting of aryl and a 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms selected from N, O, and S, wherein said aryl and said heteroaryl are optionally substituted 1, 2, or 3 times with a substituent selected from halo, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{3-6} cycloalkenyl, hydroxy, C_{1-6} alkoxy, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, and phenyl;

or (iii) R^1 and R^2 together with the nitrogen atom to which they are bonded form a 4-8 membered heterocyclic ring or a 7-11 membered bicyclic heterocyclic ring, each of said 4-8 membered heterocyclic ring and said 7-11 membered bicyclic heterocyclic ring contain 1, 2 or 3 heteroatoms selected from the group consisting of N, O, and S, and wherein either said heterocyclic ring or said bicyclic heterocyclic ring may be optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, oxo (i.e., =O), amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, and halo;

or (iv) R^2 together with the adjacent nitrogen atom and Y may form an optionally substitued nitrogen-containing heterocycle, or R^2 together with the adjacent nitorgen atom, Y, and Ar may form an optionally substitued nitrogen-containing heterocycle or salt thereof, and wherein said heterocycles are optionally substituted one to four times by at least one substituent selected

from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, oxo (i.e., =O), amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, and halo;

In another aspect of the invention, there is provided a pharmaceutical composition for use in the treatment, prophylaxis or both of one or more conditions or indications set forth herein comprising a compound of formula (I), or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier.

In a further embodiment of the invention, there are provided processes for the preparation a compound of formula (I).

Detailed Description of the Invention

As used herein, "a compound of the invention" or "a compound of formula (I)" means a compound of formula (I) or a pharmaceutically acceptable salt, solvate, of physiologically functional derivative (such as, e.g. a prodrug), thereof.

As used herein, unless otherwise specified, the term "alkyl" and "alkylene" refer to straight or branched hydrocarbon chains containing 1 to 6 carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, tert-butyl, and hexyl. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, propylene, butylene, and isobutylene. "Alkyl" also includes substituted alkyl. "Alkylene" also includes substituted alkylene. The alkyl and alkylene groups may optionally be substituted with at least one substituent selected from the group consisting of hydroxy, alkoxy, halo, amino, alkylamino, dialkylamino, thio, and cyano. Halo, alkoxy, and hydroxy are particularly preferred.

As used herein, unless otherwise specified, the term "cycloalkyl" refers to a non-aromatic carbocyclic ring having from 3 to 8 carbon atoms (unless otherwise specified) and no carbon-carbon double bonds. "Cycloalkyl" includes by way of example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. "Cycloalkyl" also includes substituted cycloalkyl. The cycloalkyl may be optionally substituted with at least one substituent

selected from the group consisting of hydroxy, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, and alkyl. Halo, hydroxy, and alkoxy are preferred.

As used herein, unless otherwise specified, the term "alkenyl" refers to straight or branched hydrocarbon chains containing 2 to 8 carbon atoms and at least one and up to three carbon-carbon double bonds. Examples of "alkenyl" as used herein include, but are not limited to, ethenyl and propenyl. "Alkenyl" also includes substituted alkenyl. The alkenyl group may be optionally substituted with at least one substituent selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halo, hydroxy, alkoxy, and cyano. Halo, hydroxy, and alkoxy are preferred.

As used herein, unless otherwise specified, the term "cycloalkenyl" refers to a non-aromatic carbocyclic ring having from 3 to 8 carbon atoms (unless otherwise specified) and up to 3 carbon-carbon double bonds. "Cycloalkenyl" includes by way of example, cyclobutenyl, cyclopentenyl, and cyclohexenyl. "Cycloalkenyl" also includes substituted cycloalkenyl. The ring may be optionally substituted with at least one substituent selected from the group consisting of cyano, halo, hydroxy, $-NH_2$, $-N_3$, -CN, $-O-C_{1-3}$ alkyl, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and $-C_{1-3}$ alkyl (including haloalkyl).

As used herein, the terms "halo" or "halogen" refer to fluorine, chlorine, bromine, and iodine. Preferred among these are chlorine (or "chloro") and fluorine (or "fluoro").

Unless otherwise specified, the term, "aryl" (as well as "aromatic") refers to monocyclic carbocyclic groups and fused bicyclic carbocylic groups having from 6 to 12 carbon atoms and having at least one aromatic ring. Examples of particular aryl groups include, but are not limited to, phenyl and naphthyl. "Aryl" also includes substituted aryl, especially substituted phenyl. An aryl ring may be optionally substituted with at least one substituent selected from the group consisting of halo, alkyl (including haloalkyl), alkenyl, cycloalkyl, cycloalkenyl, alkoxy, amino, hydroxy, hydroxyalkyl, aminoalkyl, carboxy, carboxamide, sulfonamide, heteroaryl (abbreviated as "Het"), amidine, cyano, nitro, and azido. Preferred aryl groups according to the invention include, but are not limited to, phenyl and substituted phenyl.

Preferred substituted phenyl is a phenyl containing one or more halo groups, particularly chloro and fluoro groups.

The terms "heterocycle" and "heterocyclic" refer to a ring system composed of C and at least one other atom selected from the group consisting of N, O, and S. Heterocycles may or may not be heteroaromatic as defined below. In other words, heteroaromatics are heterocycles, but all heterocycles are not heteroaromatic.

The term "heteroaryl" and "heteroaromatic" refer to a monocyclic or bicylic aromatic ring system composed of C and at least one other atom selected from the group consisting of N, O, and S.

The terms "members" (and variants thereof, e.g., "membered") in the context of heterocyclic, heteroaryl, and aryl groups refers to the total atoms, carbon and heteroatoms (N, O, and/or S) which form the ring. Thus, an example of a 6-membered heterocyclic ring is piperidine, an example of a 6-membered heteroaryl ring is pyridine, and an example of a 6-membered aryl ring is benzene.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) that occur and events that do not occur.

Formula (I) of the invention is set forth in detail as follows.

A is aryl or heteroaryl, optionally substituted one to four times with at least one substituent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano and alkylthio groups. Preferred among these substituted groups are halo, C_{1-3} alkyl, and C_{1-3} alkoxy. Most preferred are fluoro, chloro, and methoxy. In a preferred embodiment said A is substituted with a halo group, q is 0, Q^1 is carbon, Q^2 is sulfur, and R^4 is hydrogen or halo. For example, A is 4-chlorophenyl and R^3 and R^4 are each hydrogen.

In the formula, the dashed line connecting Q^2 to Q^3 represents an optional bond such that the bond between Q^2 and Q^3 are connected by a double bond; and q, r, s, and t are each independently 0 or 1.

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In formula (I), q is 0 or 1. When q is 1 the bond between Q^2 and Q^3 in formula (I) is a double bond. When q is 0 there is no Q^3 group. When q is 0 then Q^2 is N, S, or O. And when q is 1, Q^2 is C or N. When q is 1 and Q^2 is N, then s is 0 and there is no R^5 substituent.

Q^1 and Q^3 are each independently carbon (C) or nitrogen (N). In one embodiment, Q^1, Q^2, and Q^3 are each carbon and q, r, s, and t are 1. In another embodiment, Q^1 is carbon, Q^2 is sulfur, q and s are 0, and r is 1.

In the formula, r and t are each independently 0 or 1. When r and t are each independently 0, then there is no R^4 substituent. When r and t are each independently 1, Q^1 and Q^3 are each independently bonded by the group R^4. Each R^4 is the same or different and is independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamio, hydroxy, cyano, alkylthio, and halo.

In formula (I), s is 0 or 1. When Q^2 is S or O, then s is 0 and there is no R^5 group. When Q^2 is C, then s is 1 and R^5 is selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo. When Q^2 is C, preferably R^5 is hydrogen or a C_{1-3} alkyl; most preferably R^5 is hydrogen or methyl.

In formula (I), R^3 is selected from the group consisting of hydrogen, amino, C_{1-6} straight or branched alkyl, and C_{3-6} cycloalkyl. Preferably, R^3 is hydrogen or a C_{1-3} alkyl; most preferably R^3 is hydrogen or methyl.

When either or both Q^1 and Q^3 are C, then R^4 is selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo. Preferably, when either or both Q^1 and Q^3 are C, R^4 is hydrogen or C_{1-3} alkyl; most preferably R^4 is hydrogen or methyl.

When Q^2 is N, and s is 1, R^5 is selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkyl amino, hydroxy, cyano, alkylthio, and halo. When Q^2 is N, and s is 1, preferably R^5 is hydrogen or a C_{1-3} alkyl; most preferably R^5 is hydrogen or methyl.

In the formula (I), Ar is an optionally substituted fused bicyclic ring having 9 to 14 members, optionally substituted one to four times by at least one substituent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano, and alkylthio groups. That is, Ar can be a fused bicyclic ring having: (i) two aromatic rings fused together, (ii) an aromatic ring and a heteroaromatic ring fused together, (iii) two heteroaromatic rings fused together, (iv) an aromatic ring fused to a heterocyclic ring, or (v) having an aromatic ring fused to a carbocyclic ring. Preferably, Ar is selected from the group consisting of quinoline, naphthalene, benzimidazole, indole, benzothiophene, benzofuran, and benzothiazole. When Ar is a ten-membered bicyclic aromatic or ten-membered bicyclic heteroaromatic ring, then preferably Ar is quinoline or naphthalene. When Ar is a 9-membered fused bicyclic heteroaromatic ring, then preferably Ar is benzimidazole, indole, benzothiophene, benzofuran, or benzothiazole.

In the formula (I), Y is a bond or a C_{1-6} alkylene, optionally substituted as defined herein. When Ar is a ten-membered polycyclic aromatic or ten-membered polycyclic heteroaromatic ring, then preferably Y is a C_{1-3} alkylene, optionally substituted; most preferably Y is methylene ($-CH_2-$), optionally substituted. When Ar is a 9-membered fused polycyclic heteroaromatic ring, then preferably Y is a bond or a C_{1-3} alkylene, optionally substituted; most preferably Y is a bond.

In (i), R^1 and R^2 of formula (I) are each independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, phenyl, and 5- or 6-membered heterocycle, wherein said alkyl, said cycloalkyl, and said heterocycle are optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, hydroxy, oxo, alkoxy, and halo. Preferably, R^1 and R^2 are each independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, and C_{3-6} cycloalkyl. Most preferably, R^1 and R^2 are each independently selected from the group consisting of hydrogen, C_{1-3} alkyl, and C_{3-6} cycloalkyl.

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Or, in (ii), R^1 and R^2 are selected from the group consisting of aryl and a 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms selected from N, O, and S, wherein said aryl and said heteroaryl are optionally substituted 1, 2, or 3 times with at least one substituent selected from the group consisting of halo, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{3-6} cycloalkenyl, hydroxy, C_{1-6} alkoxy, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, and phenyl. Preferably, when either R^1 or R^2 is aryl or heteroaryl, the other remaining R^1 or R^2 is a hydrogen, a C_{1-6} alkyl, or a C_{3-6} cycloalkyl.

Additionally, in (iii), R^1 and R^2 together with the nitrogen atom to which they are bonded can form a 4-8 membered heterocyclic ring or a 7-11 membered bicyclic heterocyclic ring. The 4-8 membered heterocyclic ring and/or the 7-11 membered bicyclic heterocyclic ring may contain 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S. And either the heterocyclic ring or the bicyclic heterocyclic ring may be optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, oxo, and halo. Here neither group R^1 or R^2 is linked to M or L. Preferably, R^1 and R^2 together form a 5- or 6-membered heterocyclic ring or an 8- to 11-membered bicylic heterocyclic ring, having 1 or 2 heteroatoms selected from the group N, O, and S wherein said heterocyclic ring and said bicyclic heterocyclic ring may be optionally substituted up to two times with a substituent selected from the group consisting of oxo and halo.

Also additionally, in (iv), R^2 together with the adjacent nitrogen atom and Y may form an optionally substituted nitrogen-containing heterocycle, or R^2 together with the adjacent nitrogen atom, Y, and Ar may form an optionally substituted nitrogen-containing heterocycle or salt thereof. The said nitrogen-containing heterocycles are optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, oxo (i.e., =O), amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, and halo. Preferably, R^2 together with the adjacent nitrogen atom and Y form a 3-7 membered ring when Y is a C_{1-6} alkyl group. Most preferably a 5-7 membered ring is formed. The 5-7 membered ring is optionally substituted by

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at least one substitutent selected from the group consisting of phenyl, one to four C_{1-3} alkyl, hydroxy, alkoxy, oxo, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, or halo.

In one embodiment, when Ar is a 10-membered aromatic or a 10-membered heteroaromatic ring, the most preferred compounds according to this invention are selected from the group consisting of

6-(4-chlorophenyl)-3-{6-[(dimethylamino)methyl]-2-naphthyl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-[6-(pyrrolidin-1-ylmethyl)-2-naphthyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-fluorophenyl)-3-[2-(pyrrolidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-fluorophenyl)-3-[2-(piperidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(2-methyl-4,5-dihydro-1*H*-imidazol-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(2,2,6,6-tetramethylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-phenyl-3-[2-(pyrrolidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-phenyl-3-[2-(pyrrolidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one.

In another embodiment, when Ar is a 9-membered heteroaromatic ring, the most preferred compound according to this invention is

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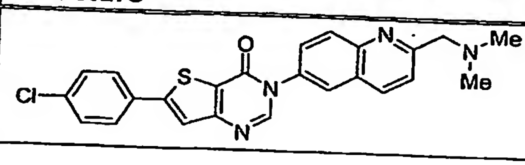
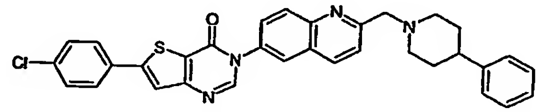
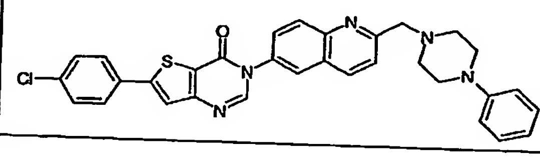
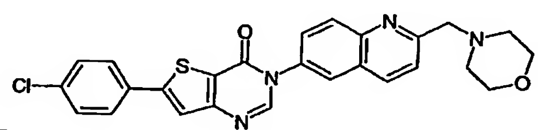
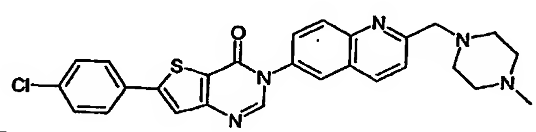
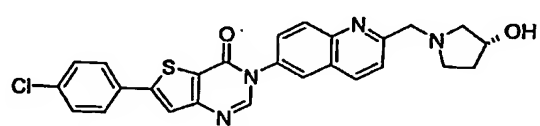
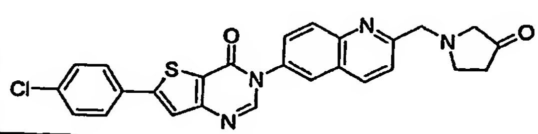
6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g., they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centers are inverted. Certain compounds of formula (I) may be prepared as regioisomers. The present invention covers both the mixture of regioisomers as well as individual compounds. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

It is to be understood that the present invention includes all combinations and subsets of the particular groups defined hereinabove. Specific compounds of formula (I) include but are not limited those set forth in Table I and/or those prepared examples herein.

Table I

Example No.	Structure	Name
1		6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one
2		6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one
3		6-(4-chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
4		6-(4-chlorophenyl)-3-[2-(morpholin-4-ylmethyl)quinolin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
5		6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
6		3-[2-(hydroxymethyl)-6-quinolinyl]-6(4-methylphenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)one
7		6-(4-chlorophenyl)-3-{2-[(3-oxo-1-pyrrolidinyl)methyl]-6-quinolinyl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

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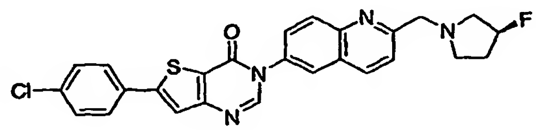
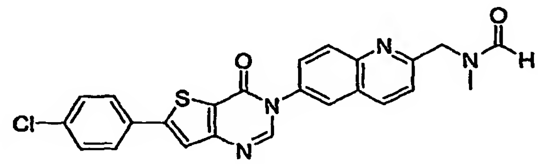
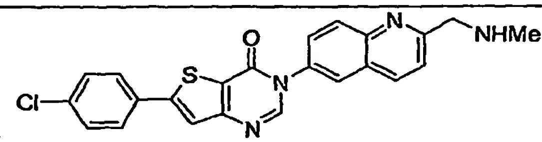
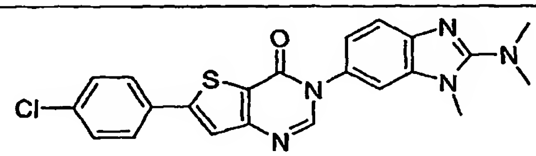
8		6-(4-chlorophenyl)-3-(2-{[(3*S*)-3-fluoropyrrolidinyl]methyl}-6-quinolinyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one
9		[6-(6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl)-2-quinolinyl]methyl(methyl)-formamide
10		6-(4-chlorophenyl)-3-{2-[(methylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one
11		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

It will be appreciated by those skilled in the art that the compounds of the present invention may also be utilized in the form of a pharmaceutically acceptable salt or solvate or physiologically functional derivative thereof (e.g., a prodrug). The pharmaceutically acceptable salts of the compounds of formula (I) include conventional salts formed from pharmaceutically acceptable inorganic or organic acids or bases as well as quaternary ammonium salts. More specific examples of suitable acid salts include maleic, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, aleic, tartaric, citric, palmoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulfonic, methanesulfonic (mesylate), naphthaliene-2-sulfonic, benzenesulfonic, hydroxynaphthoic, hydroiodic, malic, steroic, tannic, and the like.

Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically

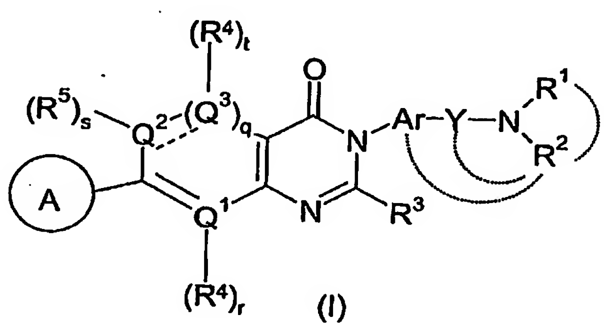
acceptable salts. More specific examples of suitable basic salts include sodium, lithium, potassium, magnesium, aluminum, calcium, zinc, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine and procaine salts.

The term "solvate" as used herein refers to a complex of variable stoichiometry formed by a solute (a compound of formula (I)) and a solvent. Solvents, by way of example, include water, methanol, ethanol, and acetic acid.

The term "physiologically functional derivative" as used herein refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, a ester or an amide of a compound of formula (I), which upon administration to an animal, particularly a mammal, such as a human, is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. See, for example, Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Vol. 1: Principles and Practice.

Processes for preparing pharmaceutically salts, solvates, and physiologically functional derivatives of the compounds of formula (I) are conventional in the art. See, e.g., Burger's Medicinal Chemistry and Drug Discovery,5th Edition, Vol.1: Principles and Practice.

Compounds of formula (I) below are conveniently prepared in accordance with the reaction schemes and/or processes outlined or described herein.



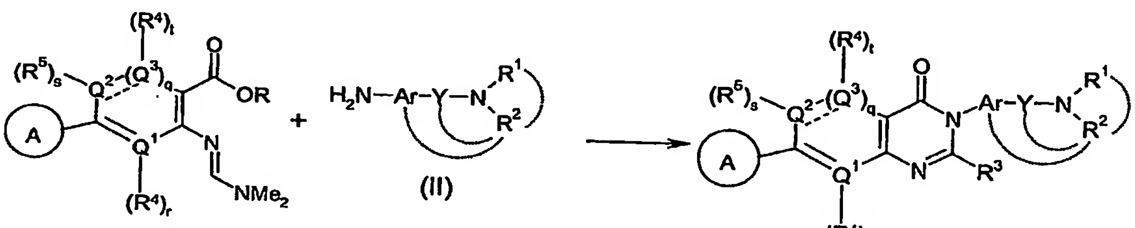
(I)

As will be apparent to those skilled in the art, in the processes described below for the preparation of compounds of formula (I), certain intermediates, may be in the form of pharmaceutically salts, solvates or

physiologically functional derivatives of the compound. With respect to any intermediate employed in the process of preparing compounds of formula (I), the terms or identifiers have the same meanings as noted above with respect to compounds of formula (I). In general, processes for preparing pharmaceutically acceptable salts, solvates and physiologically functional derivatives of intermediates are known, and the process for preparing pharmaceutically acceptable salts, solvates and physiological functional derivatives of the compounds of formula (I) are similar and set forth below.

Unless otherwise stated, A, R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t are as defined in formula (I) for all of the processes enumerated herein.

Thus, compounds of formula (I) wherein R^5 is H may be prepared by reaction of an aniline of formula (II) with a formamidine ester of formula (III) wherein R is C_{1-4} alkyl.



(III) (II) (I)

Compounds of formula (I) can also be prepared by an amide coupling of the corresponding amino acid (IV) and the desired aniline (II) in a solvent, such as methylene chloride, with amide coupling agents such as EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride), followed by cyclization in refluxing carboxylic acids, such as formic acid.

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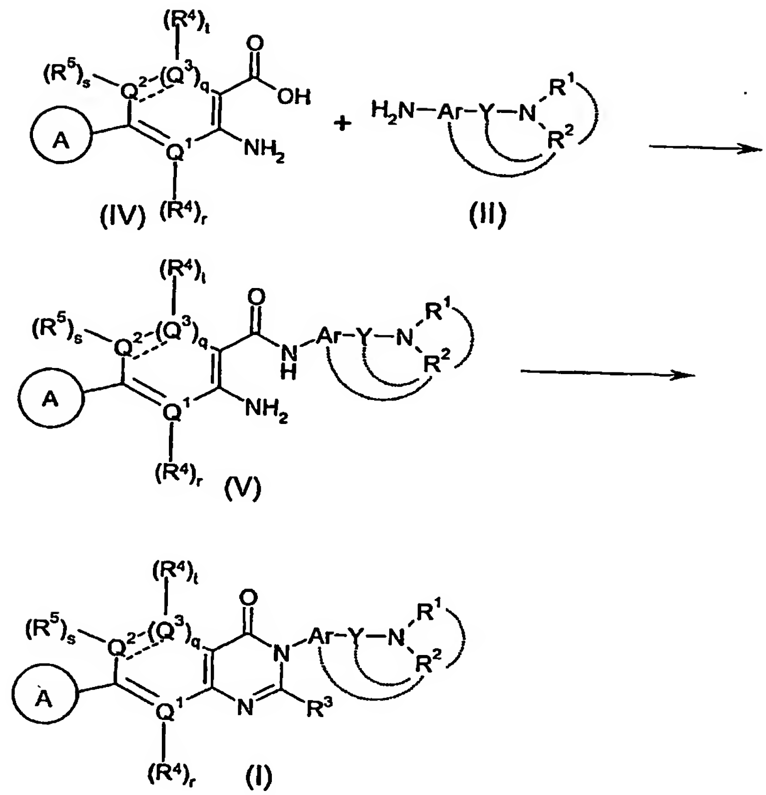
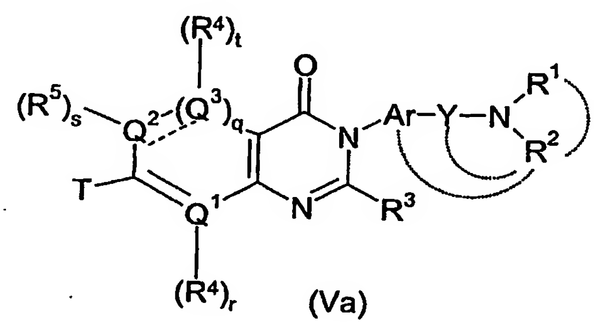


(IV) (II) (V) (I)

Compounds of formula (I) may also be prepared by reaction of a compound of formula (Va)



(Va)

with a compound capable of introducing the group A, and T is a leaving group (e.g., chloro; bromo, iodo, and triflate ($-OSO_2CF_3$)).

Thus compounds of formula (I) may be prepared from the compound of formula (Va) with a boronic acid and a palladium catalyst using a Suzuki coupling reaction or with an organostannane reagent and a palladium catalyst using a Stille coupling reaction.

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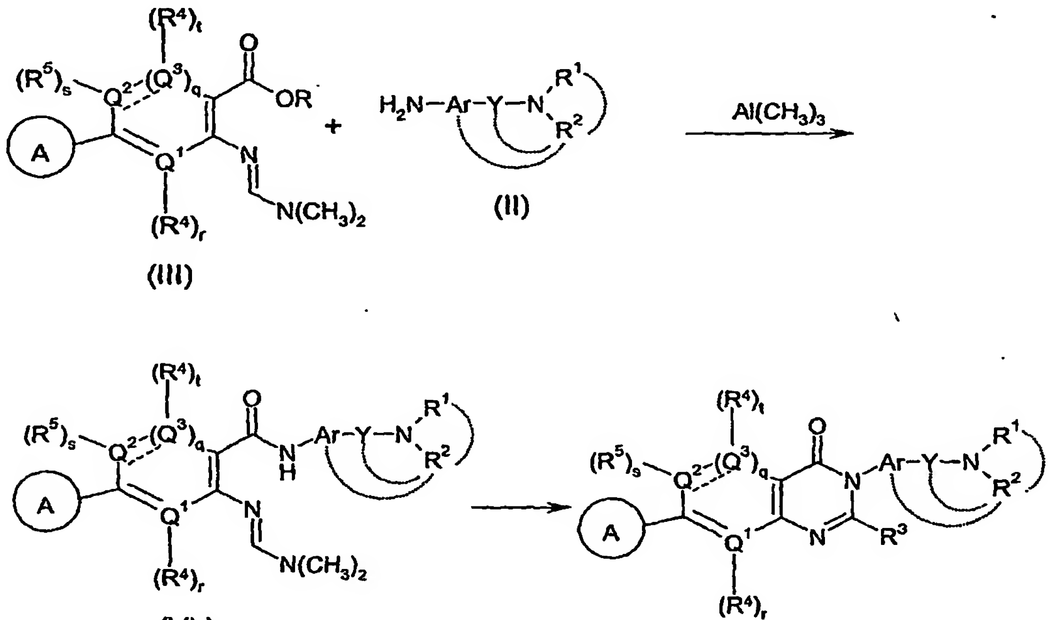
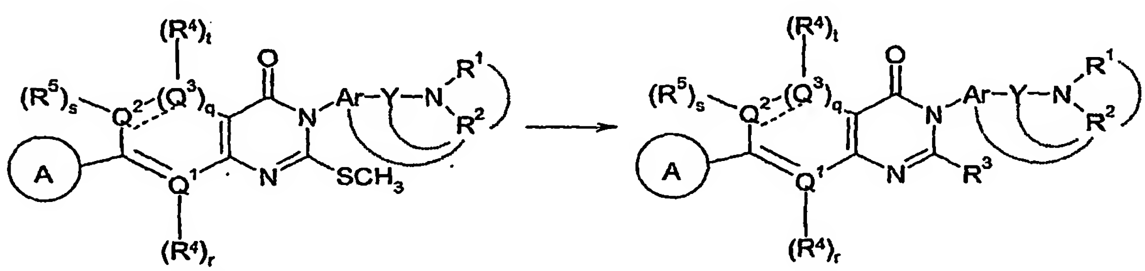
Compounds of formula (I) may also be prepared by reaction of an amino ester of formula (III) wherein R is C_{1-4} alkyl with an aniline of formula (II) in a solvent such as dichloromethane or 1,2-dichloroethane in the presence of trimethylaluminum to produce a compound of formula (Vb) and cyclizing said compound of formula (Vb).



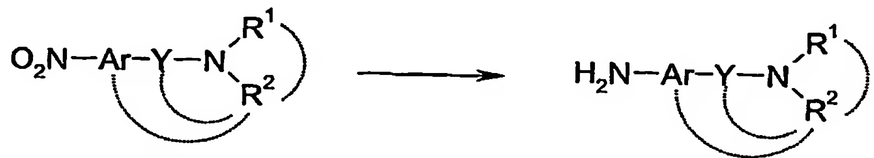
(III) (II) (Vb) (I)

Compounds of formula (I) wherein R^3 is hydrogen may also be prepared by reaction of a sulfur-containing compound such as (VI) with a reductant, such as Raney Nickel, in a solvent such as ethanol.



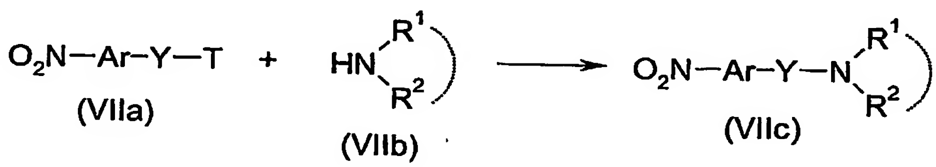
(VI) (I)

Compounds of formula (II) may be prepared by reduction of the corresponding nitroaromatic (VII) using hydrogen and a catalyst (e.g., 10% Pd on carbon), stannous chloride, or sodium dithionite.

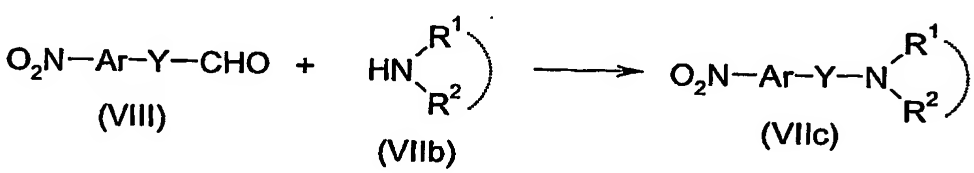


(VII) (II)

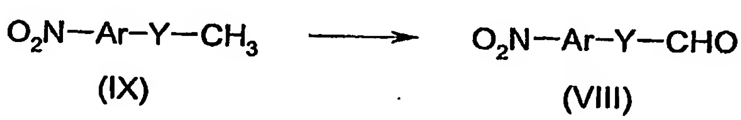
Compounds of formula VIIc wherein Y is CH_2 can be prepared from a compound (VIIa) and an amine (VIIb) and T is a leaving group (e.g., Cl, Br, I, mesylate, and tosylate).



Alternatively, compounds of this type can be made by reductive amination of an aldehyde of formula (VIII) by an amine of formula (VIIb) in the presence of a reducing agent such as a sodium borohydride.



Compounds of formula (VIII) in which Y is a bond can be prepared by reaction of a compound of formula (IX) (in which Y is a bond) with an oxidant such as selenium dioxide in a solvent such as dioxane.



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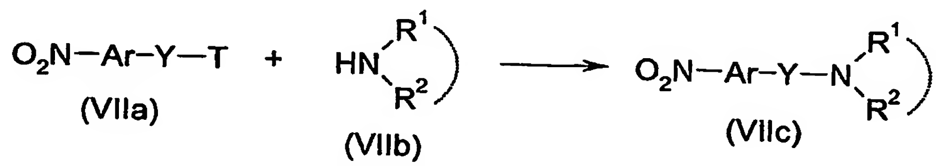
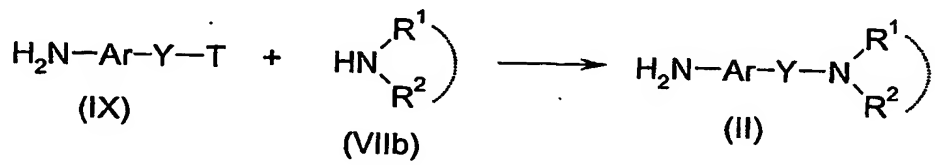
Compounds of formula VIIc can be prepared from a compound (VIIa) and an amine (VIIb) in which T is a leaving group.



Compounds of formula (II) can be prepared from a compound (IX) and an amine (VIIb) in which T is a leaving group.



In the present invention, the compounds of formula (I) are believed to have a role in the treatment of depression, anxiety, obesity and/or diabetes. Compounds of the present invention are antagonists of a MCHR1 and can be used for the treatment of a disease caused by or attributable to a melanin-concentrating hormone. Compounds of the invention may reduce hunger, suppress appetite, control eating, and/or induce satiety.

The present invention provides methods for the treatment of several conditions or diseases such as obesity, diabetes, depression (eg., major depression and/or bipolar disorder), and/or anxiety. Such treatment comprises the step of administering a therapeutically effective amount of the compound of formula (I), including a salt, solvate, or physiologically functional derivative thereof to a mammal, preferably a human. Such treatment can also comprise the step of administering a therapeutically effective amount of a pharmaceutical composition containing a compound of formula (I), including a salt, solvate, or physiologically functional derivative thereof to a mammal, preferably a human. As used herein, the term "treatment" refers to alleviating the specified condition, eliminating or reducing one or more symptoms of the condition, slowing or eliminating the progression of the condition, and

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preventing or delaying the reoccurrence of the condition in a previously afflicted or diagnosed patient or subject.

As used herein, the term "therapeutically effective amount" means an amount of a compound of formula (I) which is sufficient, in the subject to which it is administered, to elicit the biological or medical response of a cell culture, tissue, system, animal (including human) that is being sought, for instance, by a researcher or clinician.

The precise therapeutically effective amount of the compounds of formula (I) will depend on a number of factors including, but not limited to, the age and weight of the subject being treated, the precise disorder requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. Typically, the compound of formula (I) will be given for treatment in the range of about 0.1 to about 200 mg/kg body weight of recipient (animal) per day and more usually in the range of about 1 to about 100 mg/kg body weight per day. In general, acceptable daily dosages, may be from about 0.1 to about 5000 mg/day, and preferably from about 0.1 to about 2000 mg/day. Unit doses will normally be administered once or more than once per day, preferably about 1 to about 4 times per day.

The administration of compounds of the invention to an animal, particularly a mammal such as a human, may be by way of oral (including sub-lingual), parenteral, nasal, rectal or transdermal administration. Preferably oral administration is employed.

While it is possible that, for use in therapy, a therapeutically effective amount of a compound of formula (I) may be administered as the raw chemical, it is typically presented as the active ingredient of a pharmaceutical composition or formulation. Accordingly, the invention further provides a pharmaceutical composition comprising a compound of formula (I). The pharmaceutical composition may further comprise one or more pharmaceutically acceptable carriers, diluents, and/or excipients. The carrier(s), diluent(s), and/or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of formula (I) with one or more pharmaceutically acceptable carriers, diluents, and /or excipients.

Pharmaceutical formulations may be presented in unit dose form containing a predetermined amount of active ingredient per unit dose. Such a unit may contain a therapeutically effective dose of the compound of formula (I) or a fraction of a therapeutically effective dose such that multiple unit dosage forms might be administered at a given time to achieve the desired therapeutically effective dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example, by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example, by bringing into association the active ingredient with the carrier(s), diluent(s), and/or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules (including soft gelatin capsules, hard gelatin capsules, and capsules made from other polymers such as hydroxypropylmethylcellulose) or tablets; powders or granules; solutions, emulsions, or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions. For instance, for oral administration in the form of a tablet or capsule (e.g., hard, soft, elastic, gelatinous and/or non-gelatinous), the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate,

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as, for example, starch or mannitol. Flavoring, preservative, opaque, dispersing and coloring agent or dye can also be present.

Capsules are made by preparing a powder mixture as described above, and filling formed gelatin and/or non-gelatinous sheaths. Glidants and lubricants, such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, cellulosic polymers (e.g., hydrogels (HPMC, HPC, PVA), and the like), carboxymethylcellulose, polyethylene glycol, waxes, polyvinylpyrrolidone, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators (disintegrants) include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granuated by wetting with a binder such as a syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by

means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material (e.g., HPMC) and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

The drug may be dissolved or dispersed in a volatile liquid such as water or ethanol and sprayed onto nonpareil beads. A binder such as sucrose, polyvinylpyrollidone, hydroxypropylmethylcellulose, or the like may be used. After at least one coating, protective coat(s) of a polymer such as hydroxypropylmethylcellulose may be applied and/or a sustained or delayed release coating(s) may be applied. Such coated beads may optionally be compressed into tablets or filled into capsules.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of active ingredient. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax, or the like. The compound of formula (I) can also be incorporated into a candy, a wafer, and/or tongue tape formulation for administration as a "quick-dissolve" medicament. Oral dosage forms may be taken with or without water.

Additionally, the present invention comprises a compound of formula (I) in combination with at least one other species selected from the group

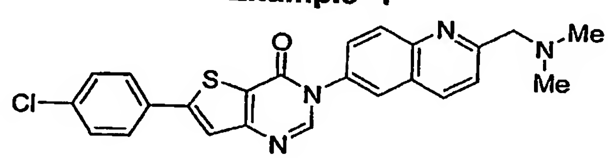
consisting of at least one agent or drug for treating obesity, diabetes (e.g., rosiglitazone and/or metformin), hypertension, and arteriosclerosis. In particular, a compound of formula (I) may be combined with at least one species for the treatment of obesity selected from the group of human ciliary neurotrophic factor, a CB-1 antagonist or inverse agonist (such as rimonabant), a neurotransmitter reuptake inhibitor (such as sibutramine, bupropion, or bupropion HCl), a lipase inhibitor (such as orlistat), an MC4R agonist, a 5-HT2c agonist, and a ghrelin receptor agonist or antagonist.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way, the invention being defined by the claims which follow.

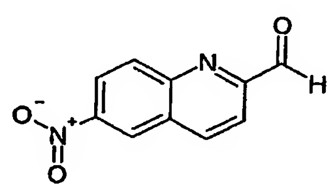
Reagents are commercially available or are prepared according to procedures in the literature.

Experimental Section

Example 1



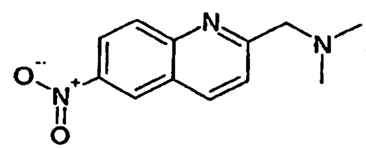
6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: 6-nitroquinoline-2-carbaldehyde

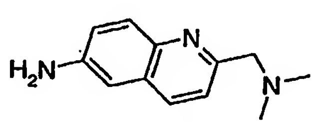
To a hot solution of selenium dioxide (41.6 g, 375 mmol) in dioxane (185 mL) and water (35 mL) was added 2-methyl-6-nitroquinoline (47.0 g, 250 mmol).

The mixture was refluxed for 30 minutes. The selenium black was filtered off and the filtrate was concentrated by rotary evaporation. The resulting solid was washed with a saturated solution of sodium bicarbonate. The solid was filtered, washed with water, and dried to give the product as a tan solid (44.8 g, 89%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H), 9.21 (d, J = 2.6 Hz, 1H), 8.97 (d, J = 8.5 Hz, 1H), 8.59 (dd, J = 2.6 Hz, J' = 9.2 Hz, 1H), 8.44 (d, J = 9.2 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H).



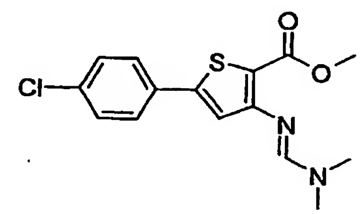
Step B: *N,N*-dimethyl-1-(6-nitroquinolin-2-yl)methanamine

To a solution of 6-nitroquinoline-2-carbaldehyde (the intermediate produced in Example 1, Step A; 44.8 g, 221 mmol) in dichloroethane (800 mL) and methanol (320 mL) was added dimethylamine (221 mL, 442 mmol, 2 M in THF) and acetic acid (13.3 g, 221 mmol). The mixture was stirred at RT for 20 min at which point sodium triacetoxyborohydride (65.6 g, 309 mmol) was added in 3 portions with vigorous mechanical stirring. The reaction mixture was stirred overnight. To the reaction mixture was added saturated sodium bicarbonate solution (300 mL) and the mixture was extracted with dichloromethane (2 x 400 mL). The organic layer was filtered through celite and washed with brine (200 mL). The organic layer was dried and concentrated to give a tan solid (41.1 g, 80% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.05 (d, J = 2Hz),.8.67 (d, J = 9.6 Hz, 1H), 8.43 (dd, J = 2.2 Hz, J' = 12.3 Hz), 8.17 (d, J = 9.2 Hz, 1H), 7.82 (d, J = 8.6 Hz, 1H), 3.75 (s, 2H), 2.24 (2, 6H):



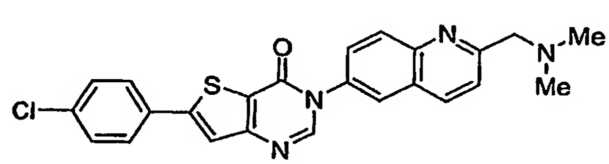
Step C: 2-[(dimethylamino)methyl]-6-quinolinamine

N,N-Dimethyl(6-nitro-2-quinolinyl)methanamine (the intermediate produced in Example 1, Step B; 365 mg, 1.58 mmol) was dissolved in EtOH. A catalytic amount of Pd/C was added. The mixture was degassed and was stirred under 1 atm H_2 for 5 h. The mix was filtered through celite and removed the solvents giving the desired intermediate (290 mg, 91%). ^{1}H NMR ($CDCl_3$): δ 2.30 (6H, s), 3.68 (2H, s), 6.87 (1H, m), 7.11 (1, m), 7.15 (1H, s), 7.43 (1H, d, J = 8.8 Hz), 7.86 (1H, m). LCMS m/z = 202 (m + H^+).



Step D: Methyl 5-(4-chlorophenyl)-3-{[(*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate

A mixture of methyl 3-amino-5-(4-chlorophenyl)-2-thiophenecarboxylate (37.3 mmol, 10.0 g) and N,N-dimethylformamide dimethyl acetal (74.7 mmol, 8.9 g) in ethanol (350 mL) was heated to reflux for 3 hours. The solvent was removed by rotary evaporation. To the residue 15 mL of toluene was added and the solvent was removed by rotary evaporation. This was repeated three times. To the resulting sticky residue, 20 mL hexanes were added followed by the gradual addition of ethyl acetate at 0°C until it solidified. The resulting solid was collected by filtration giving the dsired intermediate (11.9 g, 98.9%). ^{1}H NMR ($CDCl_3$): δ 3.08 (6H, d, J = 6.5 Hz), 3.81 (3H, s), 6.98 (1H, s), 7.35 (2H, d, J = 8.6 Hz), 7.53 (2H, d, J = 8.5 Hz), 7.69 (1H, s). LCMS m/z = 323 (m + H^+).



Step E: 6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

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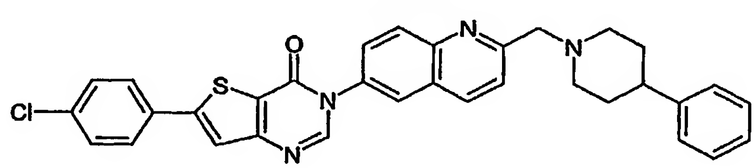
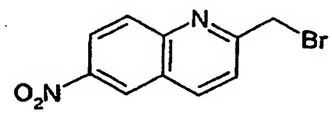
A solution of $AlMe_3$ in hexanes (0.96 mL, 1.92 mmol) was added slowly to a solution of 2-[(dimethylamino)methyl]quinolin-6-amine (the intermediate produced in Example 1, Step C; 0.34 g, 1.69 mmol) in dichloroethane (6 mL) at RT under N_2. After 15 min, a solution of methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}thiophene-2-carboxylate (the intermediate produced in Example 1, Step D; 0.50 g, 1.54 mmol) in dichloroethane (3 mL) was added and stirred at RT for 0.5 h. The solution was heated to reflux for 3 h then cooled to RT. Formic acid (6 mL) was added carefully and the mixture was heated to reflux for 4 h. Upon cooling to RT, an aqueous 1N NaOH solution (50 mL) was added followed by CH_2Cl_2 (400 mL) and water (300 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give 6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one (the title compound) as a tan solid (0.79 g) with ca. 85% purity. The solid was partially dissolved in hot $CHCl_3$ (20 mL), filtered, and concentrated. The resulting solid was dissolved in $CHCl_3$ (15 mL) and then Et_2O (25 mL) was added which produced a white precipitate. The solid was filtered and dried under vacuum to give 6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one (the title compound) as a white powder (0.33 g, 48%). The remaining impure material was subsequently purified in the same manner as described above to yield an additional 0.10 g of the title compound (63% overall yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.9 Hz, 1H), 8.25 (s, 1H), 8.21 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 2.3 Hz, 1H), 7.76 (dd, J = 2.4, 9.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.57 (s, 1H), 7.46 (d, J = 8.8 Hz, 2H), 3.83 (s, 2H), 2.37 (s, 6H). EI-LCMS *m/z* 447 (M+H).

Example 2

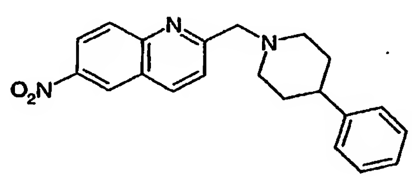


6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: 2-(bromomethyl)-6-nitroquinoline

A solution of 2-methyl-6-nitroquinoline (3.0 g, 15.9 mmol) and N-bromosuccinimide (3.11 g, 17.49 mmol) in 36 mL chloroform in a pyrex round bottomed flask, was stirred in the presence of a UV lamp at 40°C for 2 d . After cooling, the mixture was washed with aqueous sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane and the combined organic layers dried over sodium sulfate. Concentration followed by column chromatography on silica gel using hexane:ethyl acetate 7:3 afforded 2-(bromomethyl)-6-nitroquinoline as pale yellow solid (2.67 g, 63%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.78 (d, J = 8.6 Hz, 1H), 8.52 (d, J = 9.8 Hz, 1H), 8.23 (d, J = 9.2 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 4.93 (s, 2H); ES-LCMS *m/z* 267 (M+H).



Step B: 6-nitro-2-[(4-phenylpiperidin-1-yl)methyl]quinoline

To a solution of 2-(bromomethyl)-6-nitroquinoline (the intermediate produced in Example 2, Step A; 1.0 g, 3.76 mmol) in THF at room tempreature was added Hunig's base (1.31 mL, 7.52 mmol) followed by the addition of 4-phenylpiperidine (0.61 g, 3.76 mmol). The contents were stirred for 3 h at room temperature. The crude reaction mixture was concentrated and loaded directly over a silica gel column using hexane:ethyl acetate 1:1 as the eluent

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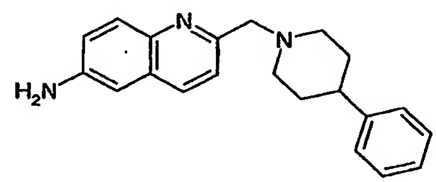
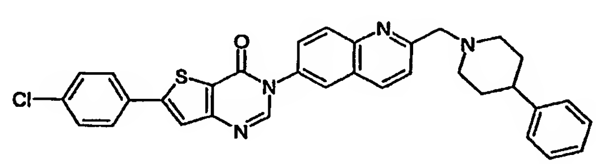
to afford 6-nitro-2-[(4-phenylpiperidin-1-yl)methyl]quinoline as a brown solid (1.05 g, 81%). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 9.03 (s, 1H), 8.67 (d, J = 9.0 Hz, 1H), 8.43 (d, J = 9.4 Hz, 1H), 8.16 (d, J = 9.4 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.29 – 7.14 (m, 5H), 3.83 (s, 2H), 2.94 (m, 2H), 2.51 (m, 2H), 2.23 (m, 2H), 1.73 – 1.67 (m, 3H); ES-LCMS *m/z* 348 (M+H).



Step C: 2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-amine

To a solution of 6-nitro-2-[(4-phenylpiperidin-1-yl)methyl]quinoline (the intermediate produced in Example 2, Step B; 1.0 g, 2.88 mmol) in 30 mL THF/EtOH (1:1) was added 0.1 g of Pd/C (10%) and the contents stirred under hydrogen gas (40 psi) for 6 h. The reaction was then filtered through celite, washed with EtOH and the contents concentrated under vacuum to afford 2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-amine as a green solid (0.8g, 87%). ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 7.91 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.39 – 7.10 (m, 6H), 6.78 (s, 1H), 3.45 (s, 2H), 2.94 (m, 2H), 2.52 (m, 2H), 2.16 (m, 2H), 1.74 – 1.65 (m, 3H); ES-LCMS *m/z* 320 (M+H).

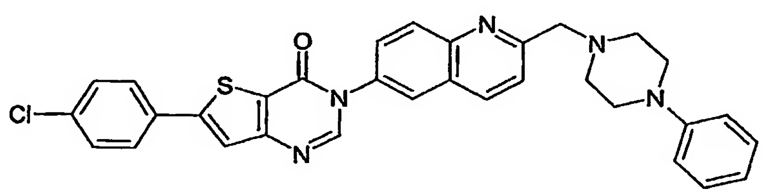


Step D: 6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one

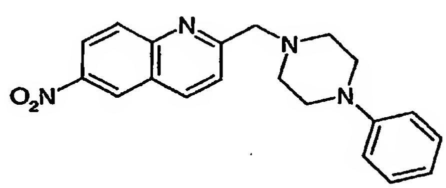
To 2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-amine (the intermediate produced in Example 2, Step C; 0.160 g, 0.506 mmol) was added methyl 5-(4-

chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene]amino}thiophene-2-carboxylate (0.163 g, 0.506 mmol) and 0.5g of phenol as the solvent. The reaction mixture was heated from 100°C to 135°C over a period of 1.5h. The crude mixture was loaded over a silica gel column using DCM/MeOH (95:5) to afford 6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one (the title compound) as a yellow solid (0.085g, 30%). ^1H NMR (300 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.59 (s,1H), 8.32 (s, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.03 – 7.90 (m, 5H), 7.60 (d, J= 8.4 Hz, 1H), 7.35 – 7.21 (m, 6H), 4.76 (s, 2H), 3.61 – 3.49 (m, 2H), 3.28 – 3.15 (m, 2H), 2.87 (m, 1H), 2.22 – 1.96 (m, 4 H); ES-LCMS *m/z* 563 (M+H).

Example 3



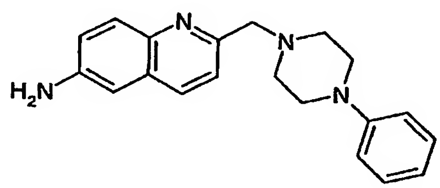
6-(4-chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one



Step A: 6-nitro-2-[(4-phenylpiperazin-1-yl)methyl]quinoline

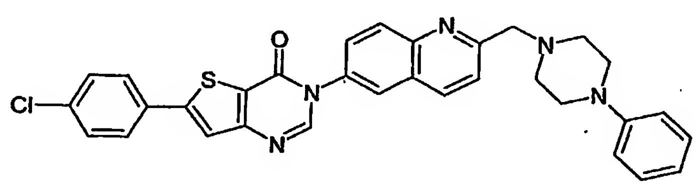
6-Nitro-2-[(4-phenylpiperazin-1-yl)methyl]quinoline was prepared using a similar experimental procedure as in Example 2, Step B by reacting 2-(bromomethyl)-6-nitroquinoline with 1-phenylpiperazine. The compound was purified by column chromatography on silica gel, eluting with a gradient of 40% ethyl acetate in hexane. ^1H NMR (300 MHz, DMSO-d_6) δ 9.05 (s, 1H),

8.69 (d, J = 8.6 Hz, 1H), 8.45 (d, J = 9.1 Hz, 1H), 8.18 (d, J = 9.1 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.20 (m, 2H), 6.92 (m, 2H), 6.77 (m, 1H) 3.87 (s, 2H), 2.61 (m, 4H), 2.48 (m, 4H); ES-LCMS *m/z* 349 (M+H).



Step B: 2-[(4-phenylpiperazin-1-yl)methyl]quinolin-6-amine

2-[(4-Phenylpiperazin-1-yl)methyl]quinolin-6-amine was prepared using a similar experimental procedure as in Example 2, Step C by reducing 6-nitro-2-[(4-phenylpiperazin-1-yl)methyl]quinoline (Example 3, Step A) with hydrogen gas and 10% Pd/C. The crude compound was used directly in the next step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.92 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.21 – 7.12 (m, 3H), 6.92 (m, 2H), 6.79 (m, 2H), 5.53 (s, 2H), 3.69 (s, 2H), 3.14 (m, 4H), 2.58 (m, 4H); ES-LCMS *m/z* 319 (M+H).

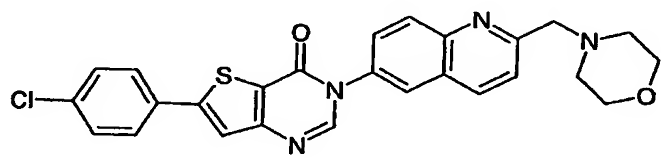


Step C: 6-(4-chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one

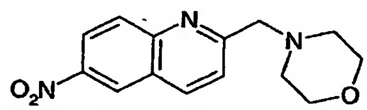
6-(4-Chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one was prepared using a similar experimental procedure as in Example 2, Step D by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene]amino}thiophene-2-carboxylate (Example 1, Step D) with 2-[(4-phenylpiperazin-1-yl)methyl]quinolin-6-amine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.60 (s,1H), 8.32 (s, 1H), 8.25 (d, J = 9.0 Hz,

1H), 8.03 – 7.94 (m, 4H), 7.84 (d, J= 8.4 Hz, 1H), 7.60 (m, 2H), 7.28 (m, 1H), 7.16 (m, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.87 (t, J = 7.2 Hz, 1H), 6.74 (d, J = 7.7 Hz, 1H), 4.84 (s, 2H), 3.54 (m, 4H), 2.07 (m, 4H); ES-LCMS *m/z* 564 (M+H).

Example 4

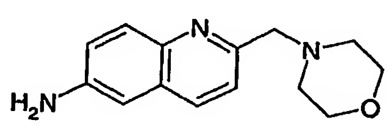


6-(4-chlorophenyl)-3-[2-(morpholin-4-ylmethyl)quinolin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one



Step A: 2-(morpholin-4-ylmethyl)-6-nitroquinoline

2-(Morpholin-4-ylmethyl)-6-nitroquinoline was prepared using a similar experimental procedure as in Example 2, Step B by reacting 2-(bromomethyl)-6-nitroquinoline with morpholine. The desired compound was purified by column chromatography on silica gel, eluting with a gradient of 80% ethyl acetate in hexane. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.72 (d, J = 8.6 Hz, 1H), 8.48 (d, J = 9.1 Hz, 1H), 8.21 (d, J = 9.2 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H), 3.89 (s, 2H), 3.66 (m, 4H), 2.54 (m, 4H); ES-LCMS *m/z* 274 (M+H).



Step B: 2-(morpholin-4-ylmethyl)quinolin-6-amine

2-(Morpholin-4-ylmethyl)quinolin-6-amine was prepared using a similar experimental procedure as in Example 2, Step C by reducing 6-nitro-2-[(4-

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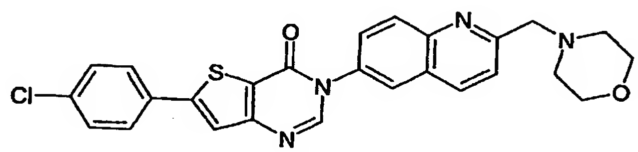
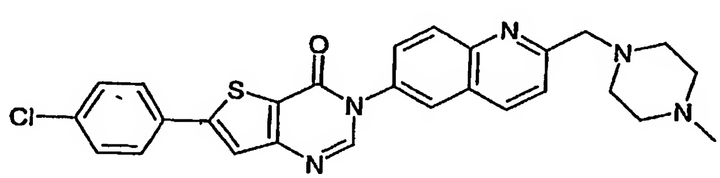
phenylpiperazin-1-yl)methyl]quinoline with hydrogen gas and 10% Pd/C. The crude compound was used directly in the next step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.21 – 7.11 (m, 1H), 6.81 (m, 1H), 5.55 (s, 2H), 3.65 (s, 2H), 3.61 (m, 4H), 2.51 (m, 4H); ES-LCMS *m/z* 244 (M+H).



Step C: 6-(4-chlorophenyl)-3-[2-(morpholin-4-ylmethyl)quinolin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one

The title compound was prepared using a similar experimental procedure as in Example 2, Step D by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate (Example 1, Step D) with 2-(morpholin-4-ylmethyl)quinolin-6-amine (Example 4, Step B). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.42 (d, J = 8.6 Hz, 1H), 8.19 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 8.01 (s, 1H), 7.95 – 7.90 (m, 3H), 7.75 (d, J = 8.4 Hz, 1H), 7.59 (m, 2H), 3.79 (s, 2H), 3.61 (m, 4H), 2.48 (m, 4H); ES-LCMS *m/z* 509 (M+H).

Example 5



6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one

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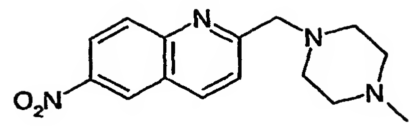
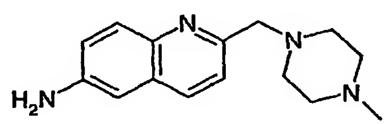


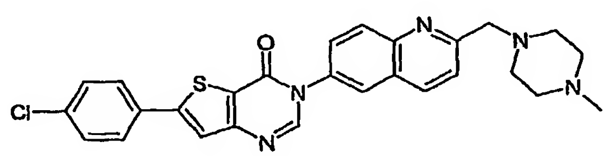
Step A: 2-[(4-methylpiperazin-1-yl)methyl]-6-nitroquinoline

2-[(4-Methylpiperazin-1-yl)methyl]-6-nitroquinoline was prepared using a similar experimental procedure as in Example 2, Step B by reacting 2-(bromomethyl)-6-nitroquinoline with 1-methylpiperazine. The desired compound was purified by column chromatography on silica gel, eluting with 100% ethyl acetate. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.73 (d, J = 8.5 Hz, 1H), 8.49 (d, J = 9.3 Hz, 1H), 8.21 (d, J = 9.3 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 3.89 (s, 2H), 2.75 (m, 4H), 2.54 (m, 4H), 2.45 (s, 3H); ES-LCMS *m/z* 287 (M+H).



Step B: 2-[(4-methylpiperazin-1-yl)methyl]quinolin-6-amine

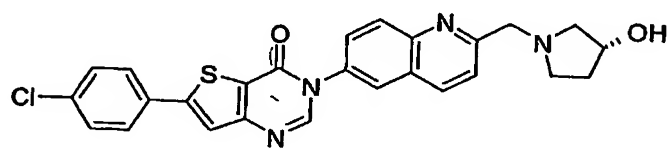
2-[(4-Methylpiperazin-1-yl)methyl]quinolin-6-amine was prepared using a similar experimental procedure as in Example 1, Step C by reducing 6-nitro-2-[(4-phenylpiperazin-1-yl)methyl]quinoline with hydrogen gas and 10% Pd/C. The crude compound was used directly in the next step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.81 (s, 1H), 5.57 (s, 2H), 3.71 (s, 2H), 2.76 (m, 4H), 2.53 (m, 4H), 2.43 (s, 3H); ES-LCMS *m/z* 257 (M+H).



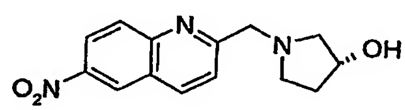
Step C: 6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one

The title compound was prepared using a similar experimental procedure as in Example 2, Step D by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate (Example 1, Step D) with 2-[(4-methylpiperazin-1-yl)methyl]quinolin-6-amine (Example 5, Step B). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.42 (d, J = 8.6 Hz, 1H), 8.19 (s, 1H), 8.11 (d, J = 9.0 Hz, 1H), 8.02 (s, 1H), 7.94 – 7.88 (m, 3H), 7.75 (d, J = 8.5 Hz, 1H), 7.59 (m, 2H), 3.82 (s, 2H), 2.64 – 2.37 (m, 11H); ES-LCMS *m/z* 502 (M+H).

Example 6



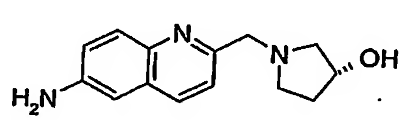
3-[2-(hydroxymethyl)-6-quinolinyl]-6(4-methylphenyl)thieno[3,2-*d*]pyrimidin-4(*3H*)one



Step A: (3R)-1[(6-nitro-2quinolinyl)methyl]-3-pyrrolidinol

This intermediate was prepared from (3R)-hydroxypyrrolidine and 6-nitroquinoline-2-carbaldehyde using the techniques described in Example 1, Step B.

^{1}H NMR (400 MHz, CDCL3) δ 8.77 (s, 1H); 8.69 (d, J = 9.6 Hz, 1H); 8.30 (d, J = 8.4 Hz, 1H); 8.17 (d, J = 9.2 Hz, 1H); 7.75 (d, J = 8.4 Hz, 1H); 4.41-4.39 (m, 1H); 4.04 (s, 2H); 3.04-2.98 (m, 1H); 2.82-2.73 (m, 1H); 2.55-2.49 (m, 1H); 2.28-2.20 (m, 1H); 1.86-1.79 (m, 1H). ES-LCMS *m/z* 296 (M+Na).



Step B: (3*R*)-1-[(6-amino-2-quinolinyl)methyl]-3-pyrrolidinol

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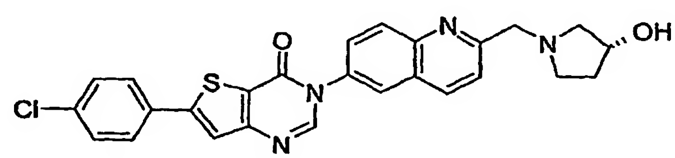
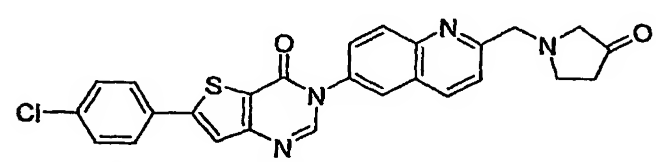
This intermediate was prepared from the intermediate produced in Example 6, Step A, by using the techniques described in Example 1, Step C.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 8.4 Hz, 1H); 7.79 (d, J = 9.2 Hz, 1H); 7.49 (d, J = 8.8 Hz, 1H); 7.29 (d, J = 9.2 Hz, 1H); 6.97 (s, 1H); 4.62 (s, 2H); 4.41(m, 1H); 3.48-3.39 (m, 2H); 3.26-3.14 (m, 2H); 2.19-2.02 (m, 1H); 1.95-1.85 (m, 1H). ES-LCMS *m/z* 244 (M+H).



Step C: 6-(4-chlorophenyl)-3-(2-{[(3*R*)-3-hydroxypyrrolidinyl]methyl}-6-quinolinyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was obtained from the intermediate produced from Example 6, Step B, by using the techniques described in Example 2, Step D.
^{1}H NMR (400 MHz, CDCL3) δ 8.23-8.17 (m, 3H); 7.89 (s, 1H); 7.74 (d, J = 8.4 Hz, 1H); 7.67-7.65 (m, 3H); 7.56 (s, 1H), 7.40 (d, J = 7.6 Hz, 2H); 4.40 (bs, 1H); 4.05 (s, 2H); 3.30-2.99 (m, 1H); 2.85-2.70 (m, 2H); 2.54-2.50 (m, 1H); 2.32-2.20 (m, 1H); 1.91-1.75 (m, 1H). ES-LCMS *m/z* 489 (M+H).

Example 7

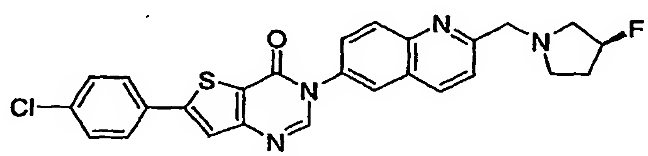


6-(4-chlorophenyl)-3-{2-[(3-oxo-1-pyrrolidinyl)methyl]-6-quinolinyl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

To oxalyl chloride (2M solution in dichlomethane, 5.5 mL, 11 mmol) at -60°C, was added DMSO (1.7 mL, 22 mmol), The resulting mixture was stirred at this temperature for 5 minutes. In a separate flask, 6-(4-chlorophenyl)-3-(2-{[(3*R*)-3-hydroxypyrrolidinyl]methyl}-6-quinolinyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (33 mg, 0.67 mmol) was dissolved in 2mL dichloromethane. The above prepared oxidant solution (1.5 mL, 0.67 mmol) was added at –60°C. After the mixture

was stirred for 15 minutes. 0.5 mL triethylamine was added. Then the mixture was let warmed up to room temperature. The reaction was quenched by pouring the reaction mixture into saturated sodium bicarbonate solution. It was then partitioned between dichloromethane and aqueous layers and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried and the solvents were removed by evaporation *in vacuo.* The residue was purified by flash chromatography eluting with 3% methanol in dichloromethane. The title compound was obtained (26 mg) as light tan solid. ^{1}H NMR (400 MHz, CDCL3) δ 8.27-8.22 (m, 3H); 7.92(s, 1H); 7.77 (d, J = 8.8 Hz, 1H); 7.69-7.66 (m, 3H); 7.57 (s, 1H); 7.46 (d, J = 8.4 Hz, 2H); 4.11(s, 2H); 3.11 (s, 2H); 3.09 (t, J = 7.2 Hz, 2H); 2.49 (t, J = 7.4 Hz, 2H). ES-LCMS *m/z* 487 (M+H).

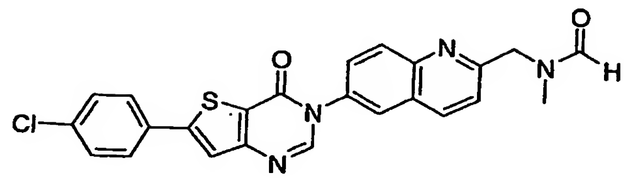
Example 8



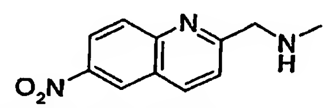
6-(4-chlorophenyl)-3-(2-{[(3*S*)-3-fluoropyrrolidinyl]methyl}-6-quinolinyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

To 6-(4-chlorophenyl)-3-(2-{[(3*R*)-3-hydroxypyrrolidinyl]methyl}-6-quinolinyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (20 mg, 0.04 mmol) in dichloroethane (1.5 mL), diethylaminosulfur trifluoride (DAST, 10 mg, 0.06 mmol) was added at -30°C. The mixture left stirring overnight while warming up to room temperature. The mixture was poured into an ice cold saturated sodium bicarbonate solution and extracted with dichlomethane. After the combined organic layers were washed and dried, the solvent was removed *in vacuo.* The residue was purified by flash chromatography eluting with 5% methanol in dichlomethane affording the title compound as solid (12 mg). ^{1}H NMR (400 MHz, CDCL3) δ 8.24-8.19 (m, 3H); 7.89(s, 1H); 7.76-7.72 (m, 2H); 7.67 (d, J = 8.4 Hz, 2H); 7.56 (s, 1H); 7.45 (d, J = 8.4 Hz, 2H); 5.30-5.13 (m, 1H); 4.05(s, 2H); 3.03-2.82 (m, 2H); 2.60 (m, 1H); 2.28-2.04 (m, 2H). ES-LCMS *m/z* 490 (M+H).

Example 9

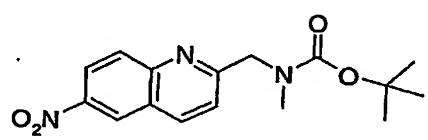


[6-(6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl)-2-quinolinyl]methyl(methyl)formamide



Step A: *N*-methyl(6-nitro-2-quinolinyl)methanamine

This intermediate was prepared from methylamine and 6-nitroquinoline-2-carbaldehyde using the techniques described in Example 1, Step B. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.02 (s, 1H); 8.64 (d, J = 8,8 Hz, 1H); 8.42 (d, J = 8.8 Hz, 1H); 8.13 (d, J = 9.2 Hz, 1H); 7.79 (d, J = 8.4 Hz, 1H); 3.98 (s, 2H); 2.32(s, 3H). ES-LCMS *m/z* 218 (M+H).



Step B: *tert*-butyl methyl[(6-nitro-2-quinolinyl)methyl]carbamate (two rotamers)

The intermediate obtained in Example 9, Step A (1.4 g, 6.45 mmol) was dissolved in dichloromethane. Triethylamine (0.91 g, 9.03 mmol) and di-*tert*-butyl dicarbonate (1.97 g, 9.03 mmol) were added. The reaction was stirred for 10 minutes and diluted with dichloromethane, washed sequentially with saturated solutions of sodium bicarbonate and sodium chloride, dried, and concentrated under reduced pressure. The resultant residue was purified by flash chromatography using a 2:1 hexane:ethyl acetate mixture as the eluent to provide 1.95 g (95% yield) of the desired intermediate as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.77 (bs, 1H); 8.46 (d, J = 9.2 Hz, 1H); 8.31 (bs, 1H); 8.14 (d, J = 8.8 Hz, 1H); 7.54-7.48 (m, 1H); 4.76 (s) and 4.72(s), total

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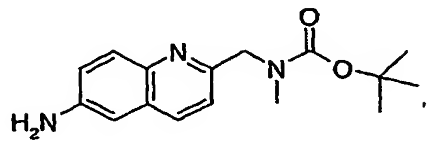
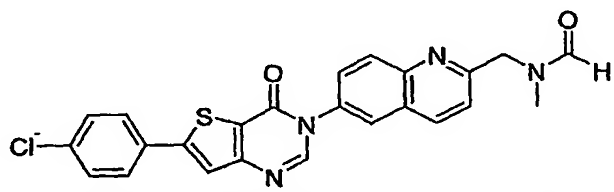
2H; 3.00(s) and 2.93 (s), total 3H; 1.51 (s) and 1.39 (s), total 9H. ES-LCMS *m/z* 318 (M+H).



Step C: *tert*-butyl (6-amino-2-quinolinyl)methyl(methyl)carbamate

This intermediate was prepared by starting with the intermediate produced in Example 9, Step B, and subjecting it to the conditions found in Example 1, Step C.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (d, J = 8.8 Hz, 1H); 8.14 (bs, 1H); 7.55-7.49 (m, 2H); 7.14 (bs, 1H); 4,81 (s, 2H); 2.96(bs, 3H); 1.40(s) and 1.18(s), total 9H. ES-LCMS *m/z* 288 (M+H).

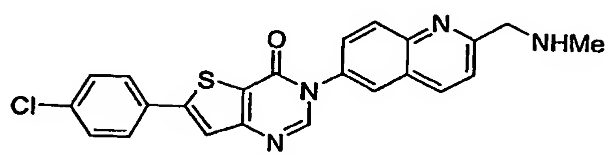


Step D: [6-(6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl)-2-quinolinyl]methyl(methyl)formamide (rotamers)

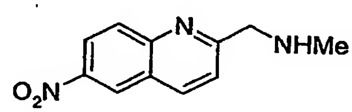
The intermediate obtained in Example 9, Step C (430 mg, 1.5 mmol) was dissolved in 1,2-dichlorethane under a nitrogen atmosphere. A 2M solution of trimethylaluminum in toluene (1.1 mL, 2.2 mmol) was added dropwise via syringe. The mixture was stirred 20 minutes at room temperature and then heated at reflux overnight. The solvent was removed under reduced pressure and the resultant residue was dissolved in formic acid and heated at reflux for 2 hours. The formic acid was removed under reduced pressure and the resultant residue was dissolved in dichlormethane, washed with a saturated solution of potassium carbonate, dried, and concentrated under reduced pressure. The resultant residue was purified by flash chromatography using a 2-3% MeOH-dichloromethane mixture as the eluent to provide the title compound (150 mg).

[1]H NMR (400 MHz, $CDCl_3$) δ 8.24-8.19 (m, 3H); 7.92 (d, J = 8.8 Hz, 1H); 7.78 (d, J = 8.8 Hz, 1H); 7.67 (d, J = 8.4 Hz, 2H); 7.57 (s, 1H); 7.50-7.40 (m, 3H); 4.87(s) and 4.74(s), total 2H;); 3.02 (s) and 2.90 (s), total 3H. ES-LCMS *m/z* 461 (M+H).

Example 10

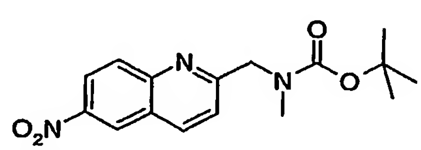


6-(4-chlorophenyl)-3-{2-[(methylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



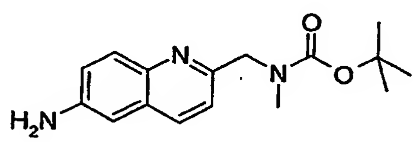
Step A: 1-(6-nitroquinolin-2-yl)methanamine

Methyl amine (7.3 mL of a 2.0 M solution in tetrahydrofuran) was added to a solution of 2-(bromomethyl)-6-nitroquinoline (0.86 g, 3.23 mmol) in 10 mL of tetrahydrofuran. The mixture was stirred at room temperature for 1.5 hours. The solvent was evaporated and the crude product was purified by chromatography on silica gel. Elution with a gradient of 0-10% methanol in dichloromethane gave 0.47 g (67%) of desired product as a brown gum. [1]H NMR (400 MHz, DMSO-d_6) δ 9.1 (s, 1H), 8.71 (d, J=8.5 Hz, 1H), 8.48 (d, J=9.2 Hz, 1H), 8.18 (d, J=9.2 Hz, 1H), 7.80 (d, J=8.5 Hz, 1H), 4.23 (s, 2H), 3.34 (br s, 1H) 2.50 (s, 3H). ES-LCMS m/z 218 (M+H).



Step B: *tert*-Butyl methyl[(6-nitroquinolin-2-yl)methyl]carbamate

Di(*tert*-butyl) dicarbonate (0.71 g, 3.24 mmol) and triethylamine (0.30mL, 2.16 mmol) were added to a partial solution of *N*-methyl-1-(6-nitroquinolin-2-yl)methanamine (0.47 g, 2.16 mmol) in 20 mL of dichloromethane. The resulting homogeneous solution was stirred at room temperature for 30 minutes. The solvent was evaporated and the residue purified by chromatography on silica gel with a gradient of 0-50% ethyl acetate in hexane to give 0.295 g (43%) of desired product as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.70 (d, J=8.6 Hz, 1H), 8.46 (d, J=9.1 Hz, 1H), 8.15 (d, J=9.3 Hz, 1H), 7.56 (m, 1H), 4.70 (s, 2H), 2.96 (m, 3H), 1.46 and 1.24 (s, 9H).



Step C: *tert*-Butyl (6-aminoquinolin-2-yl)methyl(methyl)carbamate

Palladium (5% by weight on activated carbon, 0.098 g, 0.046 mmol) was added to a solution of *tert*-butyl methyl[(6-nitroquinolin-2-yl)methyl]carbamate (0.292 g, 0.92 mmol) in 20 mL of ethyl acetate in a Fisher-Porter tube. The mixture was evacuated and flushed with nitrogen, then evacuated and filled with 50 psi of hydrogen. After 1 hour, the reaction mixture was filtered through Celite and the solvent evaporated to give 0.254 g (96%) of desired product as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J=8.4 Hz, 1H), 7.61 (d, J=9.0 Hz, 1H), 7.11 (d, J=9.0 Hz, 1H), 7.10 (d, J=8.4 Hz, 1H), 6.76 (s, 1H), 5.52 (s, 2H), 4.48 (s, 2H), 2.82 (s, 3H), 1.43 and 1.31 (s, 9H).

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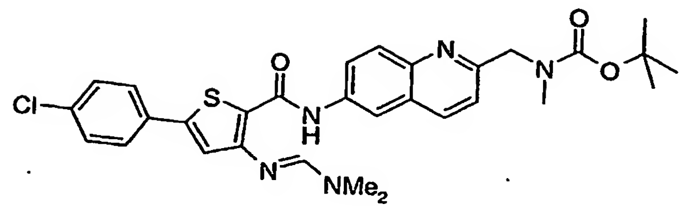
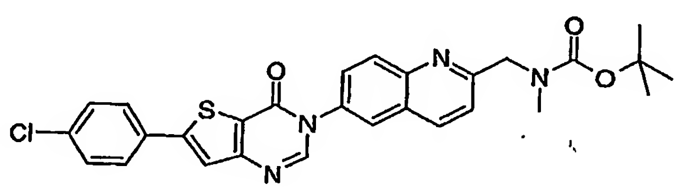


Step D: *tert*-Butyl (6-{[(5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}thien-2-yl)carbonyl]amino}quinolin-2-yl)methyl(methyl)carbamate

A solution of methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}thiophene-2-carboxylate (0.067 g, 0.209 mmol) and *tert*-butyl (6-aminoquinolin-2-yl)methyl(methyl)carbamate (0.050 g, 0.174 mmol) in 2 mL of anhydrous tetrahydrofuran was cooled to 0°C. Sodium hexamethyldisilazane (0.26 mL of a 1.0 M solution in tetrahydrofuran) was added dropwise over 5 minutes. The mixture was stirred at 0°C for 10 minutes and then allowed to warm to room temperature. After 2 hours, saturated aqueous ammonium chloride (0.5 mL) was added and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated. Chromatography on silica gel with a gradient of 0-100% ethyl acetate in hexane gave 0.029 g (24%) of desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 8.49 (s, 1H), 8.43 (d, J=2.4 Hz, 1H), 8.3 (d, J=9.0 Hz, 1H), 7.95 (d, J=9.0 Hz, 1H), 7.87 (s, 1H), 7.80 (d, J=2.4 Hz, 1H), 7.76 (1/2 Abq, J=8.6 Hz, 2H), 7.55 (1/2 Abq, J=8.6 Hz, 2H), 7.32 (m, 1H), 4.61 (s, 2H), 3.24 and 3.22 (s, 6 H), 2.90 (m, 3H), 1.46 and 1.31 (s, 9H). APCI-LCMS m/z 578 (M+H).



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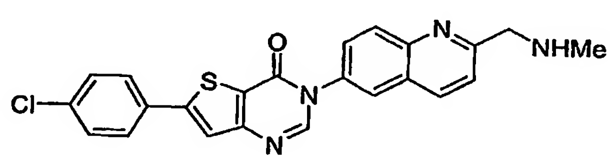
Step E: *tert*-butyl {6-[6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]quinolin-2-yl}methyl(methyl)carbamate

A catalytic amount of p-toluenesulfonic acid was added to a suspension of *tert*-butyl (6-{[(5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}thien-2-yl)carbonyl]amino}quinolin-2-yl)methyl(methyl)carbamate (0.025 g, 0.043 mmol) in 5 mL of absolute ethanol. A homogeneous solution was obtained upon heating to reflux. After 2 hours, the mixture was cooled to room temperature and the solvent was evaporated. The residue was dissolved in dichloromethane:methanol. Macroporous triethylammonium methylpolystyrene carbonate (0.050 mg, 0.14 mmol) was added, and the mixture was stirred at room temperature for 18 hours. The resin was filtered off and the solution was concentrated to give the desired product as a white solid (0.023 mg, 98%). ^1H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.44 (d, J=8.6 Hz, 1H), 8.20 (s, 1H), 8.08 (d, J=8.6 Hz, 1H), 8.01 (s, 1H), 7.94 (1/2 Abq, J=8.6 Hz, 2H), 7.90 (d, J=8.6 Hz, 1H), 7.58 (1/2 Abq, J=8.6 Hz, 2H), 7.45 (m, 1H), 4.67 (s, 2H), 2.92 (m, 3H), 1.45 and 1.28 (s, 9H). APCI-LCMS m/z 533 (M+H).



Step F: 6-(4-chlorophenyl)-3-{2-[(methylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

Trifluoroacetic acid (0.050 mL) was added to a solution of *tert*-butyl {6-[6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]quinolin-2-yl}methyl(methyl)carbamate (0.023 g, 0.043 mmol) in dichloromethane (2 mL). The mixture was stirred at room temperature for 20 hours. The solvent was evaporated and 0.5 mL of methanol, followed by 10 mL of diethyl ether was added. The mixture was filtered and the collected white solid was dried under

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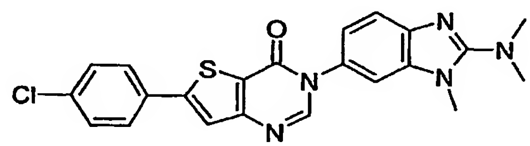
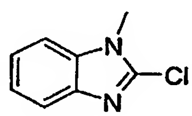
vacuum to give 0.018 g (77%) of the title compound as its trifluoroacetic acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (br s, 2H), 8.61 (s, 1H), 8.55 (d, J=8.5 Hz, 1H), 8.31 (s, 1H), 8.20 (d, J=9.1 Hz, 1H), 8.04 (s, 1H), 8.03 (d, J=9.1 Hz, 1H), 7.96 (1/2 Abq, J=8.6 Hz, 2H), 7.69 (d, J=8.5 Hz, 1H), 7.61 (1/2 Abq, J=8.6 Hz, 2H), 4.61 (s, 2H), 2.76 (s, 3H). ES-LCMS m/z 433 (M+H).

Example 11



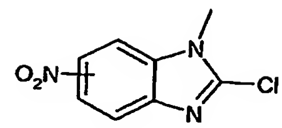
6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: 2-chloro-1-methyl-1*H*-benzimidazole

Dimethylsulfate (11mL) was added drop-wise (via addition funnel) to a solution of 2-chlorobenzimidazole (10g, 63.06mmol) and 10N NaOH(aq) (15mL) in H_2O (115mL) at 0°C. The mixture was then allowed to warm to rt, and was then stirred at rt for 2h. TLC data (50% EtOAc/Hexanes) indicated that 2-chlorobenzimidazole was consumed. A tan ppt had formed. The ppt was filtered through a buchner funnel, the filter cake washed with H_2O, and the resulting ppt was air-dried to afford a tan solid, 2-chloro-1-methyl-1*H*-benzimidazole (9.41g, 90% yield).

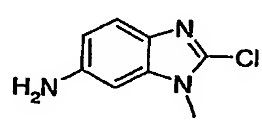
^{1}H NMR (DMSO-d6) δ 7.56 (t, 2H, J=14.5Hz), 7.26 (m, 2H), 3.76 (s, 1H). MS (+ion electrospray) 167 (100), (MH+).



Step B: mixture of 2-chloro-1-methyl-5-nitro-1*H*-benzimidazole, and 2-chloro-1-methyl-6-nitro-1*H*-benzimidazole

Conc. H_2SO_4 (20mL) was added drop-wise (via addition funnel) to a mixture of the intermediate produced in Example 11, Step A (9.41g, 56.48mmol) and conc. HNO_3 at 0°C. The mixture stirred at 0°C for 2h. TLC data (50% EtOAc/Hexanes) indicated that starting material was consumed. The reaction mixture was poured into ice water (500mL), and the resulting yellow ppt was filtered through a buchner funnel, the filter cake washed with H_2O, and the resulting ppt was air-dried to afford a yellow solid, a mixture of 2-chloro-1-methyl-5-nitro-1*H*-benzimidazole, and 2-chloro-1-methyl-6-nitro-1*H*-benzimidazole (8.78g, 73% yield).

^{1}H NMR (DMSO-d6) δ 8.65 (s, 1H,), 8.47 (s, 1H), 8.21 (d, 1H, J=11.2Hz), 8.12 (d, 1H, J=11.2Hz), 7.82 (d, 1H, J=9.0Hz), 7.77 (d, 1H, J=9Hz), 3.89 (s, 1H), 3.85 (s, 1H). MS (+ion electrospray) 212 (100), (MH+).



Step C: 2-chloro-1-methyl-1*H*-benzimidazol-6-amine

The intermediate produced in Example 11, Step B (7.78g, 36.77mmol) was added portion-wise to a solution of Sn(II)$Cl_2 \cdot 2H_2O$ (24.89g, 110.30mmol) in conc. HCl (100mL) at rt. The mixture stirred at rt for 15min, then at 100°C for 1h. TLC data (30% CH_3CN/CH_2Cl_2) indicated that starting material was consumed. The reaction mixture was cooled to rt, made pH=8 with 10N NaOH(aq), charged with Rochelle's salt (100mL), then extracted with EtOAc (4x200mL). The organics were dried over $MgSO_4$ (anhy.), filtered, and

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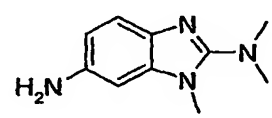
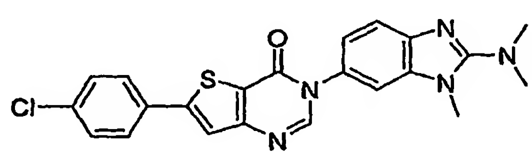
concentrated to dryness. The resulting crude was chromatographed on a SiO_2 column (0-30% CH_3CN/CH_2Cl_2 over 30min, then 30% CH_3CN/CH_2Cl_2 for 60min). Fractions corresponding to product (Rf=0.33 in 30% CH_3CN/CH_2Cl_2) were concentrated to dryness to afford a pink solid, 2-chloro-1-methyl-1*H*-benzimidazol-6-amine (2.5g, 52% yield).
1H NMR (DMSO-d6) δ 7.20 (d, 1H), 6.53 (m, 2H), 5.09 (s, 2H), 3.60 (s, 3H).
MS (+ion electrospray) 182 (100), (MH+).



Step D: N^2,N^2,1-trimethyl-1*H*-benzimidazole-2,6-diamine

A mixture of the intermediate produced in Example 11, Step C (1g, 5.51mmol) and 2M dimethylamine in MeOH (30mL) was stirred at 160°C in a sealed tube for 17.5h. TLC data (10% $MeOH/CH_2Cl_2$) indicated that starting material was consumed. The reaction mixture was cooled to rt, then concentrated to dryness. The resulting crude was chromatographed on a SiO_2 column (0-6% $MeOH/CH_2Cl_2$ over 30min, then 6% $MeOH/CH_2Cl_2$ for 30min). Fractions corresponding to product (Rf=0.34 in 10% $MeOH/CH_2Cl_2$) were concentrated to dryness to afford a pink solid, N^2,N^2,1-trimethyl-1*H*-benzimidazole-2,6-diamine (640mg, 61% yield).
^{1}H NMR (DMSO-d6) δ 7.01 (d, 1H, J=8.3Hz), 6.42 (s, 1H), 6.36 (d, 1H, J=10.3), 4.77 (s, 2H), 3.44 (s, 3H), 2.78 (s, 6H). MS (+ion electrospray) 191 (100), (MH+).



Step E: 6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

A mixture of the intermediates from Example 11, Step D (1.09g, 3.36mmol) and Example 1, Step C (640mg, 3.36mmol) was mixed in phenol (5g) and stirred from rt to 150°C over ~30min, then at 150°C for 1h. LC-MS data indicated that some starting marterial remained. Additional intermediate produced in Example 1, Step C (300mg, 0.93mmol) was added and the mixture stirred at 150°C for 1h. LC-MS data indicated that the intermediate produced in Example 11, Step D was consumed. The reaction mixture was cooled to ~60°C, then poured into MeOH (100mL). The resulting ppt was filtered, washed with MeOH, and air-dried to afford the title compound as a tan solid (1.37g, 93% yield).

1H NMR (DMSO-d6) δ 8.45 (s, 1H), 8.00 (s, 1H), 7.95 (d, 2H, J=8.5Hz), 7.58 (m, 3H), 7.47 (d, 1H, J=8.3Hz) 7.19 (d, 1H, J=10.3), 3.65 (s, 3H), 2.98 (s, 6H). MS (+ion electrospray) 436 (100), (MH+).

The activity of the compounds used in this invention may be assessed in a functional assay of MCHR1 as follows:

Materials

Black, 96-well, tissue culture-treated plates (#3904) were obtained from Corning Costar, (Cambridge, MA), LucPlus™ Luciferase Reporter Gene Assay Kit (# 6016969) was from Packard (Meriden, CT), plate seals (#097-05-00006) were from Beckman/Sagian (Fullerton, CA). DMEM/F12 medium (#11039-021), fetal bovine serum (# 16140-071), L-glutamine (#25030-081), 0.05% trypsin (# 25300-054), G418 (#10131-035) and dPBS (#4190-144) were obtained from Gibco BRL (Gaithersburg, MD). Thrombin (T7009) was obtained from Sigma Chemical Co (St. Louis, MO), MCH peptide (H-1482) was obtained from BaChem California (Torrance, CA). Chinese hamster ovary (CHO-K1) cells were obtained from the American Type Culture Collection (Rockville, MD).

Methods

CHO cells, stably expressing an elkgal4-luc^{+} reporter gene (host) were transfected by electroporation with the human melanin-concentrating hormone

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one receptor. A stable clone was selected using G418 for functional antagonist assays. MCH1R-elkgal4-luc^{+} CHO cells were propagated in complete medium (DMEM/F12, 5% FBS, 2 mM l-glutamine) in T225 flasks. Forty-eight hours prior to assay, cells were harvested with 2 mL of 0.05% trypsin, washed with complete medium and plated at a concentration of 10,000 cells/well in complete medium in black 96-well plates. Eighteen hours prior to the assay, the medium was removed from the cells by aspiration and replaced with 90 µl/well of serum-free DMEM/F12. At the time of the assay, antagonists (1 µL, 100% DMSO) as 10-point concentration curves were pipetted into the medium and plates were incubated for forty-five minutes at 37°C in a cell culture incubator. Following this incubation, 10 uL of an EC_{80} concentration of MCH was added to the medium and plates were incubated for five hours at 37°C in a cell culture incubator. The medium was aspirated by vacuum followed by the addition of 50 µl of a 1:1 mixture of LucPlus™ and dPBS/1 mM $CaCl_2$/1 mM $MgCl_2$. The aspiration step was performed in order to avoid potential assay interference by compounds which could inhibit or stimulate luciferase activity or could inhibit light signal. Plates were sealed and subjected to dark adaptation at room temperature for 10 minutes before luciferase activity was quantitated on a TopCount™ microplate scintillation counter (Packard) using 3 seconds/well count time. The ability of the antagonist to inhibit the MCH EC_{80} response was quantified by non-linear regression analysis using a curve-fitting program based in Microsoft ExCel. Specificity of the MCHR1 response was determined using the same protocol by measuring the ability of said antagonists to inhibit an EC_{80} thrombin response (endogenous) in the host cells.

The compounds described in Examples have a pIC_{50} value of greater than 7. For example, the compounds of Examples 1 and 11 have the respective MCHR1 pIC_{50} values shown below. Also included are exemplified compounds from
WO 01/82925A1 from Takeda. As can be seen from Table I, the compounds claimed herein are over 10-fold more active than the cited examples from

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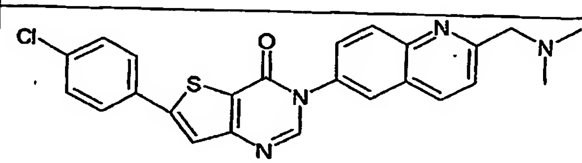
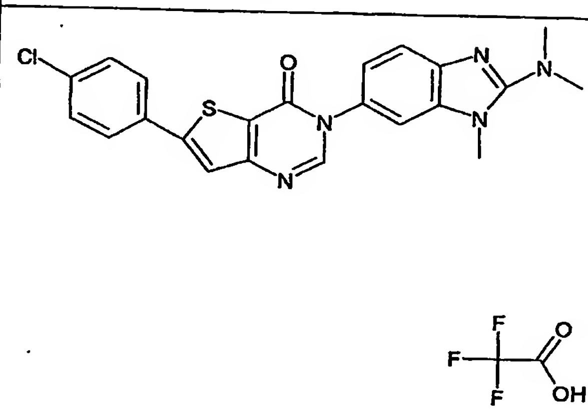
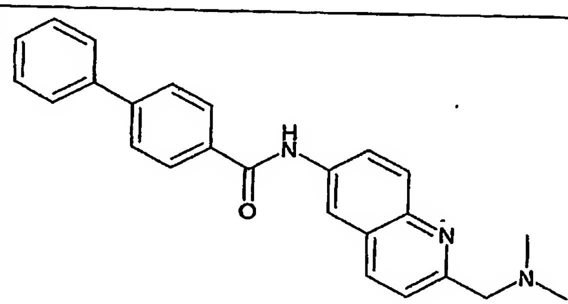
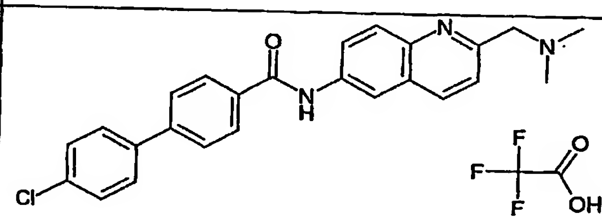
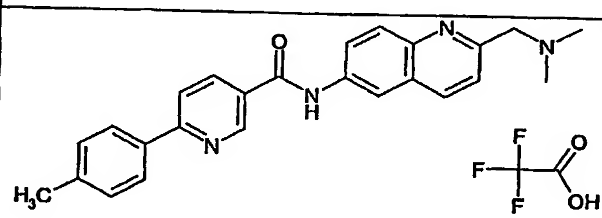
WO 01/82925A1.

Example	Structure	MCHR1 pIC_{50}
Example 1		9.1
Example 11		8.8
WO 01/82925A1 Example 15		6.3
WO 01/82925A1 Example 6 (trifluoracetic acid salt)		7.5
WO 01/82925A1 Example 17 (trifluoroacetic acid salt)		6.4

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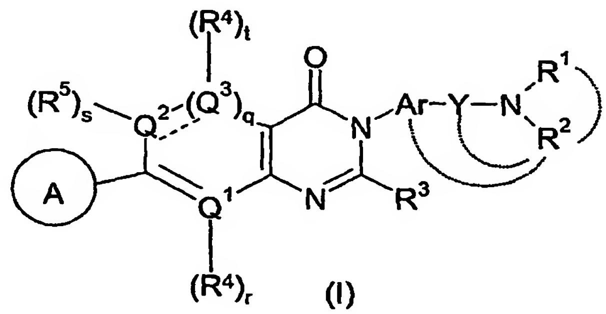
What is claimed is:

1. A compound of formula (I) comprising:



(I)

a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, wherein:

(A) is aryl or heteroaryl, optionally substituted one to four times by at least one substituent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano, and alkylthio groups;

the dashed line connecting Q^2 to Q^3 represents an optional bond;

q, r, s, and t are each independently 0 or 1;

when q is 1, the dashed line is a bond;

Q^1 and Q^3 are each independently C or N;

when q is 0 then Q^2 is N, S, or O;

when q is 1, then Q^2 is C or N; when q is 1 and Q^2 is N, then s is 0;

when Q^2 is S or O, s is 0;

when Q^1 is N, r is 0;

when Q^3 is N, t is 0;

R^3 is selected from the group consisting of hydrogen, amino, C_{1-8} straight or branched alkyl, C_{3-6} cycloalkyl, and C_{1-3} alkylthio;

when Q^1 or Q^3 is C, then each corresponding R^4 is independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo;

when q is 1 and Q^2 is C or when q is 0 and Q^2 is N, then R^5 is selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo;

Ar is an optionally substituted fused bicyclic ring;

Y is a bond or a C_{1-6} alkylene, optionally substituted;

(i) R^1 and R^2 are each independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, and a 5- or 6-membered heterocycle wherein said alkyl, said cycloalkyl, and said heterocycle are optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, oxo, alkoxy and halo;

or (ii) R^1 and R^2 are each selected from the group consisting of aryl and a 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms selected from N, O, and S, wherein said aryl and said heteroaryl are optionally substituted 1, 2, or 3 times with at least one substituent selected from halo, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{3-6} cycloalkenyl, hydroxy, C_{1-6} alkoxy, oxo, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, and phenyl;

or (iii) R^1 and R^2 together with the nitrogen atom to which they are bonded form a 4-8 membered heterocyclic ring or a 7-11 membered bicyclic heterocyclic ring, wherein said 4-8 membered heterocyclic ring and said 7-11 membered bicyclic heterocyclic ring contain 1, 2 or 3 heteroatoms selected from the group consisting of N, O, and S, and wherein either said heterocyclic ring or said bicyclic heterocyclic ring is optionally substituted one to four times by at least one substituent selected from the group consisting of by phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, oxo, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, or halo;

or (iv) R^2 together with the adjacent nitrogen atom and Y may form an optionally substitued nitrogen-containing heterocycle, or R^2 together with the adjacent nitrogen atom, Y, and Ar may form an optionally substituted nitrogen-containing heterocycle or salt thereof, wherein said heterocycle is optionally substituted one to four times by at least one substituent selected from the

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group consisting of phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, oxo, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, and halo.

2. The compound according to Claim 1 wherein said A is an aryl substituted with at least one substituent selected from the group consisting of halo, C_{1-3} alkyl, and C_{1-3} alkoxy.

3. The compound according to Claim 2 wherein A is an aryl substituted with a group selected from the group consisting of fluoro, chloro, and methoxy.

4. The compound according to Claim 1 wherein said A is a halo-substituted aryl or a halo-substituted heteroaryl; q is 0; s is 0; Q^1 is C; Q^2 is S; and R^4 is hydrogen or halo.

5. The compound according to Claim 4 wherein A is 4-chlorophenyl; and R^3 and R^4 are each hydrogen.

6. The compound according to Claim 1 wherein Q^1, Q^2, and Q^3 are each C; and q, r, s, and t are 1.

7. The compound according to Claim 1 wherein Q^1 is N; Q^2 is S; and q, r, s, and t are 0.

8. The compound according to Claim 1 wherein R^3 is hydrogen or C_{1-3} alkyl.

9. The compound according to Claim 8 wherein R^3 is hydrogen or methyl.

10. The compound according to Claim 1 wherein Ar is a 9-14 membered fused polycyclic aromatic ring or a 9-14 membered fused polycyclic heteroaromatic ring.

11. The compound of Claim 10 wherein the fused polycyclic aromatic ring or the fused polycyclic heteroaromatic ring is a ten-membered ring.

12. The compound of Claim 11 wherein said fused polycyclic aromatic ring is naphthalene or the fused polycyclic heteroaromatic ring is quinoline.

13. The compound of Claim 11 wherein Y is an optionally substituted C_{1-6} alkylene.

14. The compound of Claim 13 wherein Y is a C_{1-3} alkylene, optionally substituted.

15. The compound of Claim 14 wherein Y is methylene.

16. The compound according to Claim 1 wherein in (i), R^1 and R^2 are each selected independently from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, and C_{3-6} alkyl.

17. The compound according to Claim 16 wherein in (i), R^1 and R^2 are selected independently from the group consisting of hydrogen, C_{1-3} straight or branched alkyl, and C_{3-6} alkyl.

18. The compound according to Claim 1 wherein, in (ii), either R^1 or R^2 is aryl or heteroaryl, the other remaining R^1 or R^2 is hydrogen, C_{1-6} alkyl, or a C_{3-6} cycloalkyl.

19. The compound according to Claim 1 wherein, in (iii), R^1 and R^2 together with the nitrogen atom to which they are bonded form a 5- or 6-membered heterocyclic ring or an 8- to 11-membered bicyclic heterocyclic

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ring; having 1 or 2 heteroatoms selected from the group N, O, and S; wherein said heterocyclic ring and said bicyclic heterocyclic ring are optionally substituted up to two times with a substituent selected from the group consisting of oxo and halo.

20. The compound according to Claim 19 wherein R^1 and R^2 together with the nitrogen atom to which they are bonded form a heterocyclic ring selected from the group consisting of morpholine, piperidine, piperazine, pyrrolidine, 1,3-thiazolidine, 1H-imidazole, 4,5-dihydro-1H-imidazole, 2,3-dihydroindole, 1,2,3,4-tetrahydroquinoline, and 1,2,3,4-tetrahydroisoquinoline; and wherein said heterocyclic ring is optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, alkoxy, oxo, and halo.

21. The compound according to Claim 1 wherein, in (iv), Y is a C_{1-6} alkylene and R^2 is linked to said Y to form a 3 to 7-membered ring.

22. The compound according to Claim 21 wherein said ring is a 5 to 7-membered ring optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, alkoxy, oxo, and halo.

23. The compound according Claim 1 wherein the compound is selected from the group consisting of

6-(4-chlorophenyl)-3-{6-[(dimethylamino)methyl]-2-naphthyl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-[6-(pyrrolidin-1-ylmethyl)-2-naphthyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

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6-(4-fluorophenyl)-3-[2-(pyrrolidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-fluorophenyl)-3-[2-(piperidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(2-methyl-4,5-dihydro-1*H*-imidazol-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(2,2,6,6-tetramethylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

and 6-phenyl-3-[2-(pyrrolidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one.

24. The compound of Claim 10 wherein Ar is a 9-membered fused polycyclic heteroaromatic ring.

25. The compounds of Claim 24 wherein Ar is benzimidazole, indole, benzothiophene, benzothiazole, or benzofuran.

26. The compounds of Claim 25 wherein Y is a bond or C_{1-3} alkylene.

27. The compounds of Claim 26 wherein Y is a bond or methylene.

28. The compound according to Claim 24 wherein, in (i), R^1 and R^2 are each selected independently from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, and C_{3-6} alkyl.

29. The compound according to Claim 28 wherein, in (i), R^1 and R^2 each are selected independently from the group consisting of hydrogen, C_{1-3} straight or branched alkyl, and C_{3-6} alkyl.

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30. The compound according to Claim 24 wherein, in (ii), either R^1 or R^2 is aryl or heteroaryl, the other remaining R^1 or R^2 is hydrogen, C_{1-6} alkyl, or a C_{3-6} cycloalkyl.

31. The compound according to Claim 24 wherein, in (iii), R^1 and R^2 together with the nitrogen atom to which they are bonded form a 5- or 6-membered heterocyclic ring or an 8- to 11-membered bicyclic heterocyclic ring having 1 or 2 heteroatoms selected from the group N, O, and S; and wherein said heterocyclic ring and said bicyclic heterocyclic ring may be optionally substituted up to two times with a substituent selected from the group consisting of oxo and halo.

32. The compound according to Claim 31 wherein said ring is selected from the group consisting of morpholine, piperidine, piperazine, pyrrolidine, 1,3-thiazolidine, 1H-imidazole, 4,5-dihydro-1H-imidazole, 2,3-dihydroindole, 1,2,3,4-tetrahydroquinoline, or 1,2,3,4-tetrahydroisoquinoline; and wherein said heterocyclic ring is optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, alkoxy, oxo, and halo.

33. The compound according to Claim 24 wherein, in (iv), Y is a C_{1-6} alkylene and is linked to R^2 to form a 3-7 membered ring.

34. The compound according to Claim 33 wherein said 3-7 membered ring is a 5 to 7 membered ring optionally substituted one to four times by at least one substitutent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, alkoxy, oxo, and halo.

35. The compound according Claim 24 wherein the compound is

6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one.

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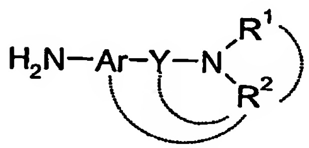
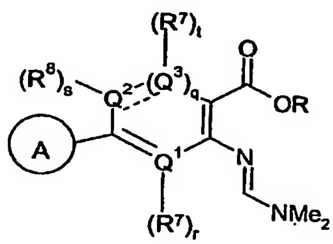
36. A process for preparing a compound of formula (I) according to claim 1 comprising reacting an aniline of formula (II)

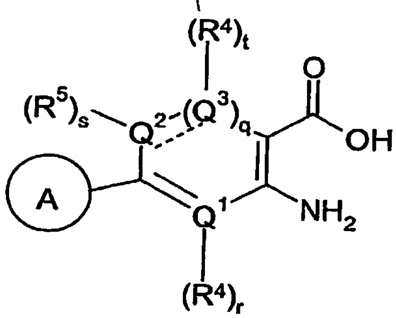

(II)

with a compound of formula (III)

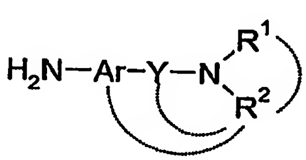

(III)

while heating in a solvent; wherein A, R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I); and R is C_1-C_4 alkyl.

37. A process for preparing a compound of formula (I) according to claim 1 comprising coupling an amino acid of formula (IV)


(IV)

with an aniline of formula (II)


(II)

in a solvent in the presence of at least one coupling agent to produce a compound of formula (V)

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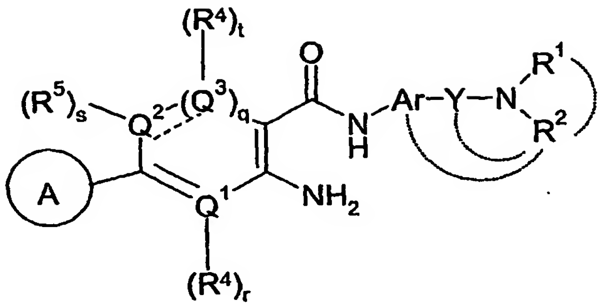
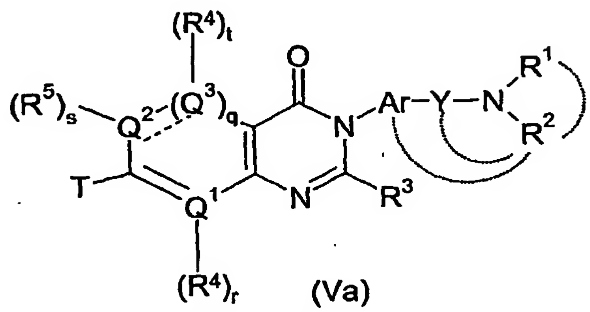


(V)

and cyclizing said compound of formula (V) to form a compound of formula (I) and wherein (A), R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I).

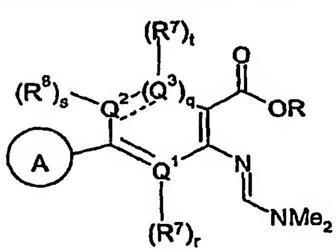
38. A process for preparing a compound of formula (I) according to claim 1 comprising reaction of a compound of formula (Va)



(Va)

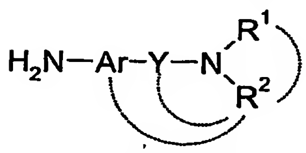
with a boronic acid and a palladium catalyst using a Suzuki coupling reaction or with an organostannane reagent and a palladium catalyst using a Stille coupling reaction and wherein (A), R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I) and T is a leaving group.

39. A process for preparing a compound of formula (I) according to claim 1 comprising coupling an amino ester of formula (III)



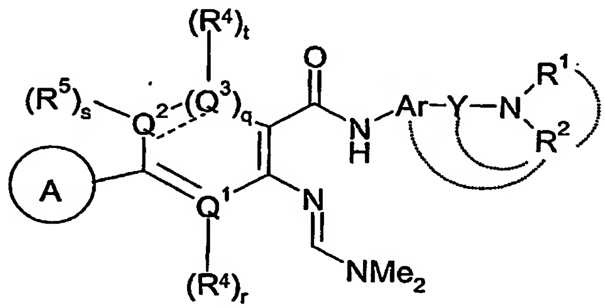
(III)

with an aniline of formula (II)



(II)

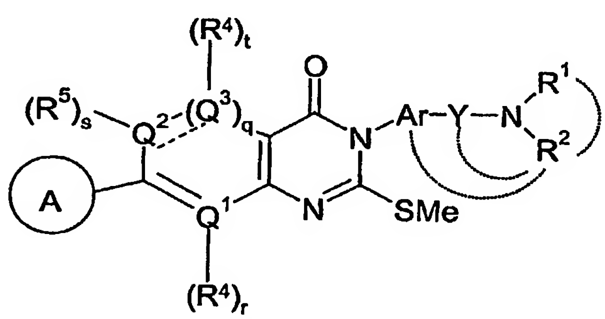
in a solvent in the presence of trimethylaluminum to produce a compound of formula (Vb)



(Vb)

and cyclizing said compound of formula (Vb) to form a compound of formula (I) and wherein wherein A, R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I).

40. A process for preparing a compound of formula (I) according to claim 1 wherein R^5 is hydrogen comprising reacting a sulfur-containing compound of formula (VI)



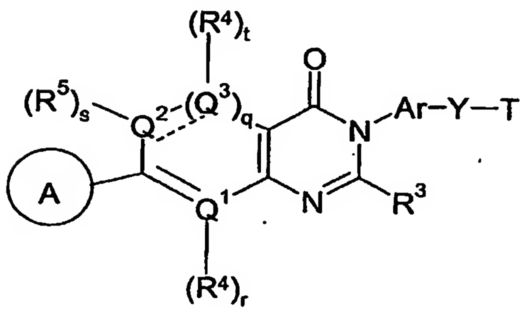
(VI)

with a Raney nickel reductant in thé presence of a solvent and wherein wherein A, R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I).

41. A process for preparing a compound of formula (I) according to claim 1 comprising the alkylation of an amine of formula (VII)

$H{-}NR^1R^2$ (VII)

with an alkylating agent of formula (VIII)



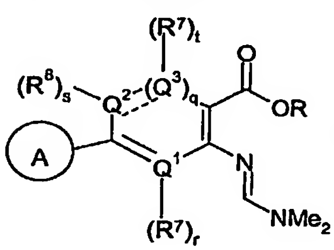
(VIII)

wherein T is a leaving group, and wherein A, R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I).

42. A process for preparing a compound of formula (I) according to claim 1 comprising the treatment of an amine of formula (VII)

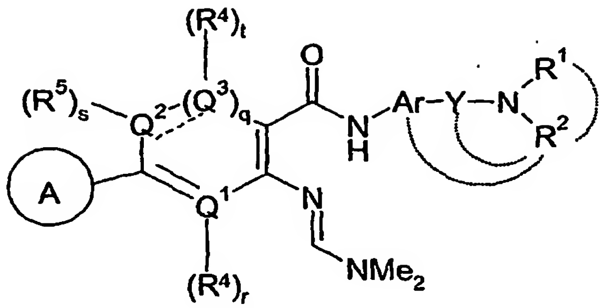
$H{-}NR^1R^2$ (VII)

with a strong base such as sodium hexamethyldisilazane and reaction with an ester of formula (III)



(III)

in a solvent such as tetrahydrofuran to produce a compound of formula (Vb)



(Vb)

and cyclizing said compound of formula (Vb) to form a compound of formula (I) and wherein wherein A, R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I).

43. A method of treating obesity, diabetes, depression, or anxiety in a mammal comprising the administration to said mammal of an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

44. The method of claim 43 wherein said mammal is a human.

45. A method of treating obesity, diabetes, depression, or anxiety in a mammal comprising the administration of an effective amount of a pharmaceutical composition containing a compound according to claim 1, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to said mammal.

46. The method of claim 45 wherein said mammal is a human.

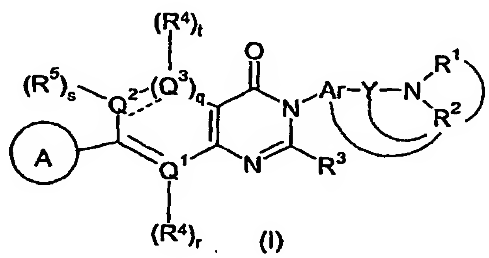
47. The compound of formula (I), a salt, a solvate, or physiologically functional derivative thereof in combination with at least one species selected from the group consisting of an agent for treating diabetes, an agent for treating hypertension, and an agent for treating arteriosclerosis.

48. The compound of formula (I), a salt, a solveat, or a physiologically functional derivative thereof in combination with at least one species for the treatment of obesity selected from the group consisting of (i) human ciliary neurotrophic factor, (ii) a CB-1 antagonist or inverse agonist, (iii) a neurotransmitter reuptake inhibitor, (iv) a lipase inhibitor, (v) an MC4R agonist, (vi) a 5-HT2c agonist, and (vii) a ghrelin receptor agonist or antagonist.

HETEROCYCLIC MCHR1 ANTAGONISTS

Abstract

This invention relates to novel heterocycles which are antagonists at the melanin-concentrating hormone receptor 1 (MCHR1), also referred to as 11CBy, to pharmaceutical compositions containing them, to processes for their preparation, and to their use in medicines. Compounds of the invention have the formula:



(I)